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(54) Title: NOVEL FUSIDIC ACID DERIVATIVES

(57) Abstract: Compounds of the general formula (I)wherein R_1 is hydrogen, halogen, $CH_¿3$, $^{CH}2?$-OH, COOH, CH_2-OSO_3,CH_2-NH-$(CH_2)_a$-R_{10}, or C(=O)-NH-$(CH_2)_a$-R¿10 ?wherein $R_{10}$is-NH_2, -NH-$(CH_2)_b$-NH_2, -NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH_2-NH-$(CH_2)_b$-NH$(CH_2)_c$-NH-$(CH_2)_d$-NH_2,-NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH-$(CH_2)_e$-NH_2, -NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH-$(CH_2)_e$NH-$(CH_2)_f$-NH_2, a saturated or unsaturated heterocycling ring comprising 1 or 2 heteroatoms, or NH-$(CH_2)_b$-R¿11, ?wherein R_{11} is a saturated or unsaturated heterocyclic ring comprising 1 or 2 heteroatoms, and a, b, c, d, e and f are the same or different and individually represent integers of from 1 to 5; R_2 is hydrogen, halogen, -OH or OR_{12}, wherein R_{12} is SO_3, C_{1-6}alkyl or C_{1-6}acyl, -NH-$(CH_2)_a$-R_{10}; R is hydrogen, halogen, a lipophilic group, -NH_2-$(CH_2)_a$-R_{10} or CH_2-NH-$(CH_2)_a$-R_{10}; R_4, R_5, R_6, R_7 and R_9 are the same or different and individually represent hydrogen, halogen, -OH, -OSO_3 or NH-$(CH_2)_a$-R_{10}; R¿3 ?and R_8 are the same or different and individually represent hydrogen, halogen, -OH or OSO_3;and the dotted lines between carbon atoms 1 and 2, 13 and 17, 16 and 17, and 17 and 20 indicate the presence of a single or double bond; provided that at least one and not more than two of R, R_1, R_2, R_4, R_5, R_6, R_7 or R_9 is NH-$(CH_2)_a$-R_{10}, CH_2-NH-$(CH_2)_a$-R_{10} or C(=O)-NH-$(CH_2)_a$-R_{10}, and the others are hydrogen, -OH or OSO_3, or (for R_2)-OR_{12}; and further provided that at least one and not more than four of R_2-R_9 are-OH or OSO_3; and pharmaceutically acceptable salts and esters thereof are active against a broad spectrum of microorganisms, and may thereof be used in the treatment of microbial infections.

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NOVEL FUSIDIC ACID DERIVATIVES

FIELD OF INVENTION

The present invention relates to novel polyaminated fusidic acid derivatives with a broad spectrum of antimicrobial activity, as well as the use of the compounds in therapy, in particular as anti-infective agents.

BACKGROUND OF THE INVENTION

In the field of antibiotics, drug resistance is an ever-increasing problem posing a serious threat to public health. The general belief for many years that infectious diseases could be controlled by the current arsenal of antibacterial drugs has resulted in the development of new and more efficient drugs getting a low priority. Recent widespread emergence of multiple resistance among pathogenic bacteria has sparked renewed interest in the discovery of new antibiotics. Although resistance to many antibiotics such as β-lactams, macrolides, tetracyclines and aminoglycosides, and the rapid spread of resistance have been recognised for many years, it was assumed that reserve drugs like glycopeptides and fluoroquinolones were sufficient to combat most infections. However, the many alarming reports of vancomycin-resistance, multiple drug resistance and examples of transfer of resistance genes between different species in the late 1980s and early 1990s has brought the issue of drug resistance to the attention of health authorities and the pharmaceutical industry.

Fusidic acid belongs to the fusidanes which is a small family of naturally occurring antibiotics having in common a tetracyclic ring system with the unique chair-boat-chair conformation separating them from regular steroids. The fusidanes therefore do not exert any hormonal activity. Fusidic acid, a fermentation product of *Fusidium coccineum*, is the most active compound of the fusidanes and is the only compound used clinically in treatment of infectious diseases. Fusidic acid (Fucidin®) is used clinically for the treatment of severe staphylococcal infections, particularly in bone and joint infections, in both the acute and the intractable form of the disease (Kuchers *et al.*, 1997 and references cited therein). It is generally given in combination with common antibiotics such as penicillins, erythromycins or clindamycin. It has also been used as an alternative to vancomycin in the control of *Clostridium difficile*.

Fusidic acid is widely used in local therapy for a number of skin and eye infections caused by staphylococci. Compared to staphylococci, all other gram-positive cocci are much less susceptible to

fusidic acid. Several streptococci including multi-resistant strains of *Streptococcus pneumoniae* are only partly resistant to fusidic acid. Other sensitive bacteria include gram-positive anaerobic cocci, such as *Peptococcus* and *Peptostreptococcus spp.*, aerobic or anaerobic gram-positive bacteria, such as *Corynebacterium diphtheriae, Clostridium tetani, Clostridium difficile* and *Clostridium perfingens*. Gram-negative bacteria are resistant except for *Neisseria spp.* and *Legionella pneumophila*. The drug is highly potent against both intracellular and extracellular *M. leprae*.

Fusidic acid exerts its antibacterial activity by blocking bacterial protein synthesis through inhibition of translocation of the ribosome relative to mRNA through interference with the "G" factor (EF-G). The exact mechanism of action is being studied on a molecular level but is so far not completely understood (Laurberg *et al.*, 2000). The difference in the mode of action of the drug explains the absence of cross-resistance between fusidic acid and common antibiotics such as penicillins and cephalosporins.

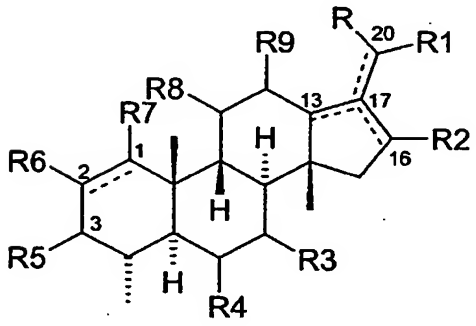
More recently, a steroidal antibiotic was isolated from the stomach of the dogfish shark, *Squalus acanthias* (Moore *et al.*, 1993; Rao *et al.*, 2000). The compound, which is based on a steroid backbone comprising a polyamine and sulphate functionality, was termed squalamine and was found to have broad-spectred antibiotic properties against gram-positive and gram-negative bacteria, fungi and protozoa. The use of native squalamine as an antimicrobial agent is disclosed in US 5,192,756. Squalamine has also been prepared by chemical synthesis although the procedure has been found to be rather cumbersome. A number of squalamine analogues and their use as antibiotics are disclosed in WO 00/09137.

Motivated by the serious difficulties in obtaining squalamine from natural sources as well as by chemical synthesis, mimics based on cholic acid derivatives have been prepared (Sadownik, *et al.*, 1995; Kikuchi *et al.*, 1997; Savage and Li, 2000; Hong-Seok, 2000). Some of these analogues have shown broad antibacterial activity, both against gram-negative and gram-positive bacteria. In addition, some of the active analogues have a very interesting synergistic effect with some known polar antibiotics. This may partly be due to assisted transport over the bacterial cell membrane by the squalamine mimic. One of the main, and probably the crucial, characteristic of the squalamine mimics having a cholic acid backbone is their relatively polar system on one surface of the steroid framework and a hydrophobic surface and a positively charged side chain on the other surface, a so-called facial amphiphile.

SUMMARY OF THE INVENTION

Compared to other antibiotics, fusidic acid has so far not developed serious problems with drug resistance. However, the substance in itself has a fairly limited antibiotic spectrum, and it might therefore be desirable to develop novel analogues based on the fusidic acid backbone, but comprising other pharmacophores than those present in the native molecule so as to exhibit an increased antibiotic actitvity against a broader range of pathogenic microorganisms. An attractive option might therefore be to prepare fusidic acid derivatives comprising a fusidic acid steroid backbone and a side chain derived from a linear polyamine, e.g. a spermine or spermidine chain of squalamine with a view to developing fusidic acid derivatives with much wider antibacterial spectrum having no cross-resistance with other clinically used antibiotics and preferably with a bactericidal action.

Accordingly, the present invention relates to a compound of the general formula I



I

wherein

R_1 is hydrogen, halogen, CH_3, CH_2-OH, COOH, CH_2-OSO_3, CH_2–NH-$(CH_2)_a$-R_{10}, or C(=O)–NH-$(CH_2)_a$-R_{10} wherein R_{10} is –NH_2, -NH-$(CH_2)_b$-NH_2, –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH_2, –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH_2, –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH-$(CH_2)_e$-NH_2, –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH-$(CH_2)_e$NH-$(CH_2)_f$-NH_2, a saturated or unsaturated heterocyclic ring comprising 1 or 2 heteroatoms, or –NH-$(CH_2)_b$-R_{11}, wherein R_{11} is a saturated or unsaturated heterocyclic ring comprising 1 or 2 heteroatoms, and a, b, c, d, e and f are the same or different and individually represent integers of from 1 to 5;

R_2 is hydrogen, halogen, -OH or –OR_{12}, wherein R_{12} is SO_3, C_{1-6} alkyl or C_{1-6} acyl, –NH-$(CH_2)_a$-R_{10};

R is hydrogen, halogen, a lipophilic group, –NH_2-$(CH_2)_a$-R_{10} or CH_2–NH-$(CH_2)_a$-R_{10};

R_4, R_5, R_6, R_7 and R_9 are the same or different and individually represent hydrogen, halogen, -OH, -OSO_3 or –NH-$(CH_2)_a$-R_{10};

R_3 and R_8 are the same or different and individually represent hydrogen, halogen, -OH or OSO_3; and the dotted lines between carbon atoms 1 and 2, 13 and 17, 16 and 17, and 17 and 20 indicate the presence of a single or double bond;

provided that at least one and not more than two of R, R_1, R_2, R_4, R_5, R_6, R_7 or R_9 is –NH-$(CH_2)_a$-R_{10}, CH_2–NH-$(CH_2)_a$-R_{10} or C(=O)–NH-$(CH_2)_a$-R_{10}, and the others are hydrogen, -OH or –OSO_3, or (for R_2) –OR_{12}; and further provided that at least one and not more than four of R_2-R_9 are –OH or –OSO_3; and pharmaceutically acceptable salts and esters thereof.

Compounds of formula I have been found to exert antimicrobial activity across a much broader range of microorganisms than fusidic acid, including activity against gram-positive bacteria such as *Streptococcus pyrogenes*, *Staphylococcus aureus*, including multidrug resistant strains, and *Staphylococcus epidermidis*, gram-negative bacteria such as *Pseudomonas* and *Escherichia coli*, yeast such as *Candida albicans* and *Saccharomyces cerevisiae* and fungi such as *Aspergillus flavus* and *Aspergillus niger*. The level of activity is equal to or better than that reported for naturally occurring squalamines (Moore *et al*, 1993; Kikuchi *et al.*, 1997; Rao *et al.*, 2000) and the most potent of the known squalamine mimics, SM-7 (Kikuchi *et al.*, 1997).

The exact mechanism of action of the present compounds is currently unknown. Without wishing to be limited to a particular hypothesis, it is believed that they may perforate cell membranes, and that membrane lysis could occur through pore formation. In this way, the present compounds may be able to circumvent two major drug resistance mechanisms, i.e. enzymatic degradation in the cell and export pathways (Sadownik *et al.*, 1995; Savage and Li, 2000 and references cited therein).

In another aspect, the invention relates to a pharmaceutical composition comprising a compound of formula I together with a pharmaceutically acceptable excipient or diluent, and to the use of compounds of formula I as medicaments.

In a further aspect, the invention relates to the use of a compound of formula I in the manufacture of a medicament for the prevention or treatment of infection.

In a still further aspect, the invention relates to a method of preventing or treating infection, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In the present context, the term "alkyl" is intended to indicate a univalent radical derived from straight or branched alkane by removing a hydrogen atom from any carbon atom. The term includes the subclasses primary, secondary and tertiary alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, n-pentyl, isopentyl, n-hexyl and isohexyl.

The term "alkoxy" is intended to indicate a radical of formula OR', wherein R' is alkyl as defined above, e.g. methoxy, ethoxy, propoxy, butoxy, etc.

The term "alkoxycarbonyl" is intended to indicate a radical of formula –COOR' wherein R' is alkyl as defined above, e.g. methoxycarbonyl, ethoxycabonyl, n-propoxycarbonyl, isopropoxycarbonyl, etc.

The term "cycloalkyl" is intended to indicate a saturated cycloalkane radical, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "cycloalkenyl" is intended to indicate monounsaturated cyclic hydrocarbon radicals, e.g. cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

The term "aryl" is intended to include radicals of carbocyclic aromatic rings, in particular 5- or 6-membered rings, optionally fused bicyclic rings, e.g. phenyl or naphthyl. The term "heteroaryl" is intended to include radicals of heterocyclic aromatic rings, in particular 5- or 6-membered rings with 1-3 heteroatoms selected from O, S and N, or optionally fused bicyclic rings with 1-4 heteroatoms, e.g. pyridyl, tetrazolyl, thiazolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thienyl, pyrazinyl, isothiazolyl, benzimidazolyl and benzofuranyl.

The term "saturated or unsaturated heterocyclic ring comprising 1 or 2 hetero atoms " is intended to indicate heteroaryl , as defined above, and compounds such as pyrrolidinyl, pyrrolinyl, imidazolidinyl, pirazolidinyl, piperidyl, piperazinyl, morpholinyl, tetrahydropyranyl, tetrahydrofuranyl.

The term "acyl" refers to a radical of formula R'-CO-, wherein R' is alkyl as indicated above.

The term "aralkyl" is intended to indicate an aromatic ring with an alkyl side chain, e.g. benzyl.

The term "halogen" is intended to indicate fluoro, chloro, bromo or iodo.

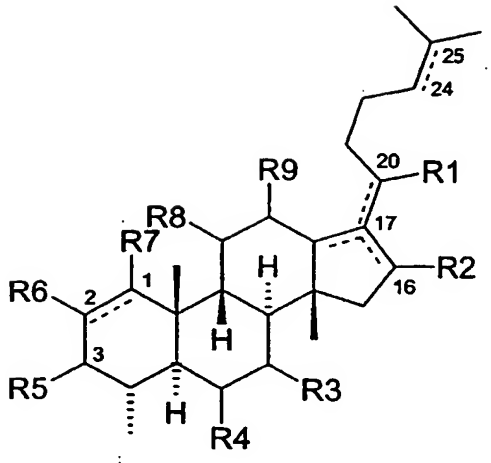
The term "polyamine building block" is intended to indicate compounds of the formula H_2N-$(CH_2)_a$-R_{10} or H_2N-$(CH_2)_a$-NH-$(CH_2)_b$-R_{11}, wherein a, b, R_{10} and R_{11} are as defined for formula I.

The term "pharmaceutically acceptable salt" is intended to indicate alkali metal or alkaline earth metal salts, for instance sodium, potassium, magnesium or calcium salts, as well as silver salts and salts with bases such as ammonia or suitable non-toxic amines, e.g. lower alkylamines, for instance triethylamine, hydroxy-lower alkylamines, for instance 2-hydroxyethylamine or bis-(2-hydroxyethyl)amine, cycloalkylamines, for instance dicyclohexylamine, or benzylamines, such as N,N'-dibenzylethylenediamine and dibenzylamine, as well as salts with suitable organic or inorganic acids, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, phosphoric, acetic, lactic, maleic, phtalic, citric, propionic, benzoic, glutaric, gluconic, metanesulfonic, salicylic, succinic, tartaric, toluenesulfonic, sulfamic or fumaric acid.

The term "pharmaceutically acceptable esters" is intended to indicate easily hydrolysable esters such as alkanoyloxyalkyl, aralkanoyloxyalkyl, aroyloxyalkyl, e.g. acetoxymethyl, pivaloyloxymethyl, benzoyloxymethyl esters and the corresponding 1'-oxyethyl derivatives, or alkoxycarbonyloxyalkyl esters, e.g. methoxycarbonyloxymethyl esters and ethoxycarbonyloxymethyl esters and the corresponding 1'-oxyethyl derivatives, or lactonyl esters, e.g. phthalidyl esters, or dialkylaminoalkyl esters, e.g. dimethylaminoethyl esters. Easily hydrolysable esters include *in vivo* hydrolysable esters of the compounds of formula I. Such esters may be prepared by conventional methods known to persons skilled in the art, such as method disclosed in GB patent No. 1 490 852 incorporated herein by reference.

Preferred embodiments of the compound of formula I

Preferred compounds of formula I are compounds of formula Ia



I_a

wherein

R1 is CH_3, CH_2–NH-$(CH_2)_a$-R_{10} or C(=O)–NH-$(CH_2)_a$-R_{10}, wherein R_{10} and a are as indicated above; R_2 and R_5 are hydrogen, -OH or –OSO_3, or, for R_2, –OR_{12}, wherein R_{12} is as indicated above; R_3, R_4, R_6, R_8 and R_9 are hydrogen, -OH or –OSO_3; and the dotted line between carbon atoms 1 and 2, 13 and 17, 16 and 17, 17 and 20, 24 and 25 indicates the presence of a single or double bond; provided that at least one and not more than four of R_2, R_3, R_4, R_5, R_6, R_8 and R_9 are –OH or OSO_3.

It is currently believed that the present fusidic acid derivatives having a lipophilic sterol backbone may form an intramolecular hydrogen bond (R_5 = OH) or salt bridge (R_5 = OSO_3) between the cationic terminus of the polyamine side chain and a hydroxy or sulphate group elsewhere in the molecule (analogous to that shown for squalamine mimics in Kikuchi *et al.*, 1997 *supra*, and references cited therein), thus imparting a circular conformation to the molecule. It is therefore preferred that at least one of R_2, R_3, R_4, R_4, R_5, R_6, R_8 or R_9 is –OH or –OSO_3 so as to make bridge formation possible. The relative positions of the polyamine side chain and the sulphate group are also thought to be important for the activity and/or potency of the compounds. When the polyamine side chain is located in position R_1, the –OH or –OSO_3 group is preferably located in position R_5 so that the molecule is brought into the desired circular (active) conformation.

There are several chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of stereoisomers with R or S configuration at each chiral centre. General formula I and Ia, and (unless specified otherwise) all other formulae in this specification are to be understood to

include all such stereoisomers in pure form and as mixtures (for example stereoisomeric mixtures) except where the configuration is expressly indicated.

In the formulas herein plain lines depict bonds which may be above or below the plane of the drawing; bonds to atoms above the plane are shown with a bold wedge starting from an atom in the plane of the drawing at the narrow end of the wedge; and bonds to atoms below the plane are shown with short parallel (wedged) lines. Substituents above the plane are described as β and shown as a bold wedge, those below the plane are described as α and shown by a line with short parallel (wedged) lines. In the compounds of formula I and Ia, it would appear that a 17α side chain is more favourable than the 17β configuration which could be due to a preferred circular conformation of the active compound.

In preferred embodiments of the compounds of the invention, a is 2 or 3.
R_{10} is preferably $-NH-(CH_2)_b-NH_2$, wherein b has the meaning indicated above, in particular 3 or 4.

R_{10} may also be $-NH-(CH_2)_b-NH-(CH_2)_c-NH_2$, wherein b and c are as indicated above, in particular wherein c is 2 or 3.

In a further preferred embodiment, R_{10} is $-NH-(CH_2)_b-NH-(CH_2)_c-NH-(CH_2)_d-NH_2$, wherein b, c and d are as indicated above, in particular wherein d is 2, 3 or 4.

In a still further embodiment, R_{10} may be $-NH-(CH_2)_b-NH-(CH_2)_c-NH-(CH_2)_d-NH-(CH_2)_e-NH_2$, wherein b, c, d and e are as indicated above, in particular wherein e is 2, 3 or 4.

In specific embodiments, R_1 may be $CH_2-NH-(CH_2)_3-NH-(CH_2)_4-NH-(CH_2)_3-NH_2$, $-NH-(CH_2)_3-NH-(CH_2)_4-NH-(CH_2)_3-NH_2$, or $C(=O)-NH-(CH_2)_3-NH-(CH_2)_4-NH-(CH_2)_3-NH_2$.

R_2 in formula I or Ia is preferably hydrogen or $-OR_{12}$, wherein R_{12} is C_{1-6} alkyl or C_{1-6} acyl, or wherein R_{12} is $-NH-(CH_2)_a-R_{10}$, $CH_2-NH-(CH_2)_a-R_{10}$ or $C(=O)-NH-(CH_2)_a-R_{10}$, wherein R_{10} and a are as indicated above.

In formula I or Ia, R_3, R_5 and/or R_8 are preferably an –OH group. In particular, R_5 and R_8 are both an –OH group, or R_5 may in addition be a $-OSO_3$ group.

In the compounds of formula I, R is preferably a lipophilic group, i.e. a group which is predominantly non-polar. Such a group is present in native fusidic acid at this position and may be of significance to the ability of the compound to lodge in cell membranes which are also lipophilic in nature. Examples of such lipophilic groups are branched or straight C_{1-10} alkyl, aryl or C_{3-8} cycloalkyl, C_{3-8}cycloalkenyl and aralkyl with 1-10 carbon atoms in the alkyl moiety, C_{1-10} alkylaryl, C_{1-10} alkyl-C_{3-8} cycloalkyl, C_{1-10} alkyl-C_{3-8} cycloalkenyl, C_{1-10} alkoxy or heteroaryl. Preferably, the lipophilic group R is the side chain found in native fusidic acid (as shown in formula Ia), or a closely related alkyl group.

Examples of compounds of the present invention are selected from the group consisting of

21-*N*-{3'-aminopropyl}-fusid-21-amide (Compound 101),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl}-fusid-21-amide (Compound 102),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-fusid-21-amide (Compound 103),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-fusid-21-amide (Compound 104),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-fusid-21-amide (Compound 105),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-fusid-21-amide (Compound 106),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-fusid-21-amide (Compound 107),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-fusid-21-amide (Compound 108),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-fusid-21-amide (Compound 109),

21-*N*-{6'-[(6'-aminohexyl)amino]hexyl}-fusid-21-amide (Compound 110),

21-*N*-{8'-[(8'-aminooctyl)amino]octyl}-fusid-21-amide (Compound 111),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-fusid-21-amide (Compound 112),

3-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-fusidic acid (Compound 113)

3-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-fusidic acid (Compound 114)

3-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]fusidic acid (Compound 115)

21-*N*-{2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl)amino}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 116),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 117),

21-*N*-{6'-aminohexyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 118),

21-*N*-{3'-aminopropyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 119),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 120),

21-*N*-{4'-[(3'-aminopropyl)amino]butyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 121),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 122),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 123),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 124),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 125),

21-*N*-{6'-[(6'-aminohexyl)amino]hexyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 126),

21-*N*-{8'-[(8'-aminooctyl)amino]octyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 127),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 128),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 129),

21-*N*-{6'-aminohexyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 130),

21-*N*-{3'-[3'-aminoproyl)amino]propyl }-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 131),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl }-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 132),

21-*N*-{2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 133),

21-*N*-{2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl)amino}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 134),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 135),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 136),

21-*N*-{4'-[(3'-aminopropyl)amino]butyl }-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 137),

21-*N*-{[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 138),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-16(17)-en-17,20,24,25-tetrahydrofusidan-21-carboxamide (Compound 139),

21-*N*-{6'-aminohexyl}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 140),

21-*N*-{6'-aminohexyl }-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 141), (C-20 epimer of Compound 140),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 142),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 143),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 144),

21-*N*-{[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 145),

21-*N*-{[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 146),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 147),

21-*N*-{2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl)amino}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 148),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 149),

21-*N*-{6'-aminohexyl}-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 150),

21-*N*-{3'-[3'-aminoproyl)amino]propyl }-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 151),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 152),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 153),

21-*N*-{4'-[(3'-aminopropyl)amino]butyl }-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 154),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 155),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 156),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 157),

21-*N*-{6'-aminohexyl}-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 158),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl}-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 159),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 160),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 161),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 162),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 163),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 164),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 165),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 166),

21-*N*-{6'-aminohexyl}-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 167),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 168),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 169),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 170),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 171),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 172),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 173),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 174),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 175),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 176),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 177),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 178),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 179),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 180).

Naming of the above mentioned compounds is based on IUPAC for the branched polyamine side chain and on fusidane conventions for the steroid moiety. Naming has been assisted by using the program available at http://www2.acdlabs.com/ilab/

Pharmaceutical compositions

Compositions of the invention comprise as an active component at least one compound of formula I or Ia (hereinafter referred to as the active ingredient) including acceptable salts and esters thereof, and optionally together with a pharmaceutically acceptable vehicle and/or diluent.

In said composition, the proportion of active ingredient to vehicle may vary from 0.5% to 100% by weight, in particular from about 0.1 to about 50% by weight. The compositions can be worked up to various pharmaceutical forms of presentation such as granulates, tablets, pills, dragees, suppositories, capsules, sustained-release tablets, suspensions, injection and may be filled in bottles or tubes or similar containers in accordance with accepted principles of pharmaceutical formulation, e.g. as disclosed in *Remington: The Science and Practice of Pharmacy*, 19th Ed., Mack Publishing Company, 1995. Pharmaceutical organic or inorganic, solid or liquid carriers and/or diluents suitable

for oral, enteral, parenteral or topical administration can be used to make up compositions containing the present compounds: Water, gelatine, lactose, starch, magnesium stearate, talc, vegetable and animal oils and fats, benzyl alcohol, gum, polyalkylene glycol, petroleum jelly, cocoa butter, lanolin, and other emulsifying agents, salts for varying the osmotic pressure or buffers for securing an appropriate pH-value of the composition can be used as auxiliary agents.

Furthermore, the composition may contain other therapeutically active components which can appropriately be administered together with the compounds of the invention in the treatment of infectious diseases such as other suitable antibiotics, in particular such antibiotics which may enhance the activity and/or prevent development of resistance. Such antibiotics include penicillins, cephalosporins, tetracyclines, rifamycins, erythromycins, lincomycin, clindamycin and fluoroquinolones. Other compounds which advantageously may be combined with the compounds of the invention, especially in topical preparations, include e.g. corticosteroids, such as hydrocortisone or triamcinolone. Alternatively, such other therapeutically active component(s) may be administered concomitantly (either simultaneously or sequentially) with the composition of the invention.

For granulates, tablets, capsules or dragees the pharmaceutical composition of the invention appropriately contains from 25% to 98% of the active ingredient of the invention, and in oral suspensions the corresponding amount is appropriately from 2% to 20 % active ingredient.

When the active ingredient is administered in the form of salts with pharmaceutically acceptable non-toxic bases, preferred salts are for instance easily water-soluble or slightly soluble in water, in order to obtain a particular and appropriate rate of absorption.

As indicated above, the compounds of formula I and Ia and their salts may be included in pharmaceutical formulations, including suspensions, ointments and creams. A pharmaceutical preparation for oral administration may also be in form of a suspension of the active ingredient as such or in the form of a sparingly water-soluble pharmaceutically acceptable salt, the preparation containing from 20 to 100 mg per ml of vehicle. A pharmaceutical preparation for topical treatment may be in the form of an ointment or cream containing the active ingredient in an amount of from 0.5 to 50% of preparation. Topical preparations are favourable due to the stability towards sunlight and the relatively lipophilic nature of the present compounds.

The dose of the compounds of the invention may suitably be selected so that the desired activity may be achieved without serious adverse effects. In the human systemic therapy the compounds and their

salts are conveniently administered (to adults) in dosage units containing no less than 50 mg and up to 1000 mg, preferably from 200 to 750 mg, calculated as the compound of formula I.

By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active ingredient alone or in admixture with one or more solid or liquid pharmaceutical diluents or vehicles.

In the form of a dosage unit, the compound may be administered one or more times a day at appropriate intervals, always depending, however, on the condition of the patient, and in accordance with the prescription made by the medical practitioner.

Thus in systemic treatment a daily dosage will preferably be an amount of from 0.5 to 3 g of the active ingredient.

The term "usage unit" in connection with topical use means a unitary, i.e. a single dose capable of being administered topically to a patient in an application per square centimetre of the infected area of from 0.1 mg to 10 mg and preferably from 0.2 mg to 1 mg of the active ingredient in question.

If the composition is to be injected, a sealed ampoule, a vial or a similar container may be provided containing a parenterally acceptable sterile aqueous or oily injectable solution or dispersion of the active ingredient as the dosage unit.

The parenteral preparations are in particular useful in the treatment of conditions in which a quick response to the treatment is desirable. In the continuous therapy of patients suffering from infectious diseases, the tablets or capsules may be the appropriate form of pharmaceutical preparation owing to the prolonged effect obtained when the drug is given orally, in particular in the form of sustained-release tablets.

In the treatment of infectious diseases, such tablets may advantageously contain other active components as mentioned above.

In the method of treating patients suffering from infectious disease, the compound of formula I or Ia or an equivalent amount of a salt thereof may suitably be administered to patients in a dose of from

0.03 g to 0.7g/kg body weight per day in 1 to 3 doses, preferably from 0.5 g to 3 g per day. Preferably, the active ingredient is administered in the form of dosage units as indicated above.

Biological activity

In vitro investigations have shown a relatively high potency of compounds of the invention against all bacteria including gram-positive and gram-negative strains (*Staphylococci, Streptococci, Corynebacteriae, Mycobacteriae, Proteus, Propionibacterium, Pseudomonas, Neisseriae, E. coli*) and fungal strains (*Candida* and *Aspergillus*). Biological tests have showed superior activity of some compounds of the invention when compared with that reported for several natural squalamine analogues (WO 00/09137). The antibacterial activity of polyaminated fusidic acid analogues is also comparable to that of related compounds reported in the literature (Moore *et al*, 1993; Kikuchi *et al.*, 1997; Rao *et al.*, 2000) and to known broad spectrum antibiotics such as ampicillin (Kikuchi *et al.*, 1997). In addition, the studies of post-antibiotic effects point towards a strong bactericidal effect of the compounds of the invention. Table 1 shows MIC (Minimum Inhibitory Concentration) values of compounds of the invention towards a number of bacterial and fungal strains. The potency of new polyaminated fusidic acid analogues is estimated by comparing the inhibition of growth of different microorganisms produced by known concentrations of the analogue to be examined and a reference compound such as fusidic acid. The microbiological assay set up is in agreement with the European Pharmacopoeia 3rd edition (1997). It is an agar diffusion method where the same volume of the tested solution is added to cavities in agar. The inhibition zones are function of the concentration of the fusidic acid analogue used. All assays are run with fusidic acid as reference substance.

Table 2

Microorganism/ strain	Selected compounds of the invention and their in vitro activities MIC (mg/l)															
	121	123	125	131	133	145	146	152	154	172	173	177	180	FA	Line-zolid	Mupi -rocin
S. aureus CJ247	4	4	1	4	4	1	1	4	4	4	4	1	1	0.02	1	0.5
S. aureus CJ200	4	4	1	4	4	1	1	4	4	4	4	1	1	0.02	4	1
S. aureus CJ234R	4	4	1	4	4	4	1	4	4	1	1	1	1	0.02	16	1
S. aureus CJ234F	4	4	1	4	4	1	1	4	4	4	4	1	1	16	1	0.5
S. aureus N6	16	4	1	4	4	1	1	4	4	4	4	4	1	16	--	--
S. epidermis CK5	4	4	1	4	4	1	1	2	1	4	1	1	4	0.02	0.25	0.04
Propionibacterium acnes FN33	4	4	1	4	4	1	1	--	--	1	4	1	1	0.2	1	--
Corynebacterium xerosis FF	4	4	1	4	4	1	1	1	0.5	4	4	1	1	0.1	--	--
Streptococcus pyogenes EC88	16	4	4	4	4	4	1	--	--	4	4	4	16	16	4	1
Streptococcus faecium EI19	16	4	16	4	4	4	1	--	--	--	--	--	--	--	--	--
E. coli HA165	16	16	16	16	16	4	4	4	8	4	4	16	16	>64	--	--
Pseudomonas aeruginosa BA17	--	16	16	4	16	4	16	8	16	4	4	16	64	>64	--	--
Saccaromyces cervisiae ZZ7	16	16	16	16	32	4	4	>125	>125	64	4	125	125	>64	--	--
Candida albicans ZA	16	16	16	16	32	>125	>125	>125	>125	64	125	64	64	>64	--	--
Asbergillus niger ZM35	64	4	16	16	32	>125	>125	>125	>125	64	125	16	4	>64	--	--

Comment:
Very clear inhibition zones for all compounds listed in table 2 indicate bactericidal action.

FA = fusidic acid

-- = mising MIC value

Strains:
FF = *Corynebacterium xerosis*
EC88 = *Streptococcus pyrogenes*
CJ234(F)=*Staphylococcus aureus* (MRSA#, Fus. resistant)
CJ(N6) = *Staphylococcus aureus* (Fus. resistant)
CJ247 = *Staphylococcus aureus*
CJ234(R) = *Staphylococcus aureus* (MRSA#, Rifampicin resistant)
CJ1200 = *Staphylococcus aureus*
CK5 = *Staphylococcus epidermidis*

#MRSA: meticilline resistant *S. aureus*

BA17 = Pseudomonas
HJ = Proteus
EI119(P) = Streptococcus faecium (Penicillin resistant)
ZA = *Candida albicans*
HA165 = *E.coli*
ZZ7 = *Saccharomyces cerevisiae*
FN33 = Propionibacterium
ZM6 = *Aspergillus flavus*
ZM35 = *Aspergillus niger*

The invention is further illustated in the following Preparations and Examples

PREPARATIONS AND EXAMPLES

General

The following standard abbreviations are used throughout this disclosure:

Ac = acetyl

Et = ethyl

Ether = diethyl ether

DCC = dicyclohexylcarbodiimide

DMF = dimethylformamide

HPLC = high performance liquid chromatography

Me = methyl

THF = tetrahydrofuran

TLC = Thin Layer Chromatography

TMS = tetramethylsilyl

TEMPO = 2,2,6,6-tetrametyl-1-piperidinyloxy free radical

NMR spectra were recorded at 300° K on either a Bruker ARX300 or a Bruker DRX500 spectrometer equipped with a 5 mm qnp and a 5 mm broad band probe, respectively.

CD_3OD or $CDCl_3$ was used as solvent. All chemical shift are given in ppm δ scala using tetramethylsilane (TMS δ = 0.00 ppm) as internal reference.

Conventional ^1H, ^{13}C and DEPT135 spectra were obtained on most compounds.

Mass spectra were recorded on either a Micromass LC-QuattroII, or a high resolution Micromass AutoSpec sector instrument.

All reactions were conducted in pre-dried glass glassware under an atmosphere of argon and transfer of reagents were carried out using syringes. All solvents and reagents were of highest available quality and used as such with the exception of some liquid polyamine building blocks of moderate purity which were distilled prior to use. Reactions could be monitored by TLC analyses using 0.25 mm glass-coated silica plates (E. Merck 60 F254). Chromatography was performed on silica gel 60, 230-400 mesh (E. Merck) using mixtures of ethyl acetate and low boiling petroleum ether (succinimide esters)or mixtures of dichloromethan, methanol and aqueous ammonia as eluant (polyamines: compounds of the invention). Compounds were alternatively purified by reversed phase (RP-18) preparative HPLC using acetonitrile buffered with trifluoroacetic acid. All purified

compounds were freeze-dried from water yielding white amorphous powder. Anhydrous solvents were prepared by storing analytical grade solvents over 4Å molecular sieves a few days prior to use. The water content was measured before use on a Carl Fisher apparatus (typical water content: 5-12 ppm for chloroform and THF).

Preparations:

Fusidic acid type starting materials

The starting fusidic acid related analogues can be prepared according to various literature procedures starting from natural fusidanes like fusidic acid, helvolic acid, viridominic acids and compounds from the cephalosporin P family (see *e.g.* Godtfredsen and Vangedal, 1962; Arigoni *et al.*, 1964; Godtfredsen *et al.*, 1965_a and 1965_b; Godtfredsen *et al.*, 1966; Diassi *et al.*, 1966; von Daehne *et al.*, 1979 and references cited therein) and by similar chemical modifications of the above-mentioned including hydrogenation of double bonds, dehydration reactions, sulphatation, acetylation, desacetylation and oxidations, well known to those skilled in the art.

Polyamine building blocks

Polyamine building blocks are generally chosen from those commercially available, *e.g.* those found in the Available Chemicals Directory (ACD) database, but can also be synthesised by methods known from the literature including such reactions as direct alkylation of amines, reductive amination and catalytic hydrogenation of amides to the corresponding amines (selected references describing various synthetic methods for the preparation of polyamine building blocks: Goodnow *et al.*, 1990; Bergeron *et al.*, 1994; Strømgaard *et al.*, 1999; Gaell and Blagbrough, 2000; Kuksa *et al.*, 2000 and references cited therein; Karigiannis and Papaioannou, 2000 and references cited therein).

General methods:

Preparation of compounds in which the polyamine building block is linked to C-21 of fusidic acid by an amide bond

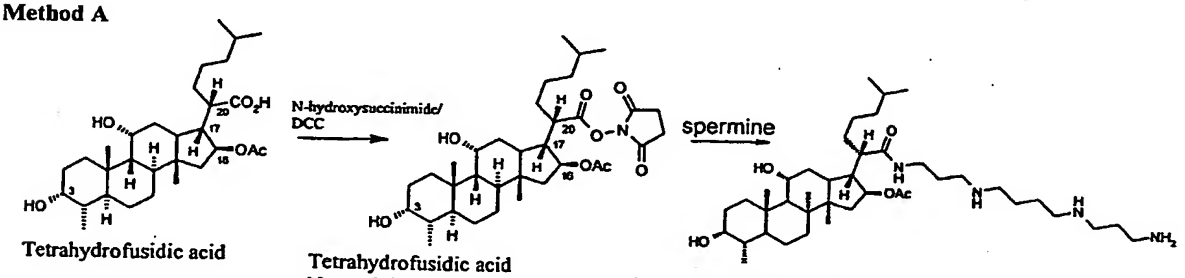
Compounds of the invention where the polyamine building block is linked to the fusidane nucleus via an amide bond may be prepared from various steroids containing a carboxylic acid, e.g. from tetrahydrofusidic acid in scheme 1, and numerous polyamine building blocks as defined above. The carboxylic acid group of a fusidic acid derivative is first esterified to produce a reactive ester, for example a succinimide ester of by reacting the carboxylic acid group with N-hydroxysuccinimide in

anhydrous THF in presence of dicyclocarbodiimide (Kikuchi *et al.*, 1997). The succinimide ester may then be reacted with a polyamine building block by dissolving an excess of the polyamine in anhydrous chloroform under argon and then slowly adding a chloroform solution containing the activated ester (Kikuchi *et al.*, 1997). The reactions are performed at room temperature and are completed between 6 and 24 hours. After this time the reaction mixture can be concentrated without additional aqueous work-up procedures and directly purified by reversed phase HPLC using mixtures of acetonitrile and water buffered with trifluoroacetic acid as eluent or column cromatography on silica gel using mixtures of dichloromethan, methanol and aqueous amonia as eluent. All compounds of the invention obtained using method A could be prepared using the reaction conditions described hereinafter for Compound 125.

Preparation of Compound 125 using general method A, Scheme 1

The method is illustrated by an example in Scheme 1 where the fusidic acid nucleus is represented by tetrahydrofusidic acid. Tetrahydrofusidic acid is first converted to the corresponding succinimide ester by reaction with N-hydroxysuccinimide in anhydrous THF in presence of dicyclocarbodiimide. Spermine (3 equivalents) in anhydrous chloroform under argon is then slowly added over a period of 30 min to a chloroform solution containing tetrahydrofusidic acid N-succinimide ester. The reaction mixture is stirred at room temperature for 16 h after which time chloroform is evaporated under reduced pressure resulting a pale yellow oil. Pure Compound 125 is obtained after chromatography on silica gel using a mixture of dichloromethan, methanol and 25% aqueaous ammonia as eluent. A white powder of pure Compound 125 is obtained after freeze drying of purified product in yields ranging from 60-90%.

Method A



Scheme 1. General example for the preparation of compounds of the invention using method A.

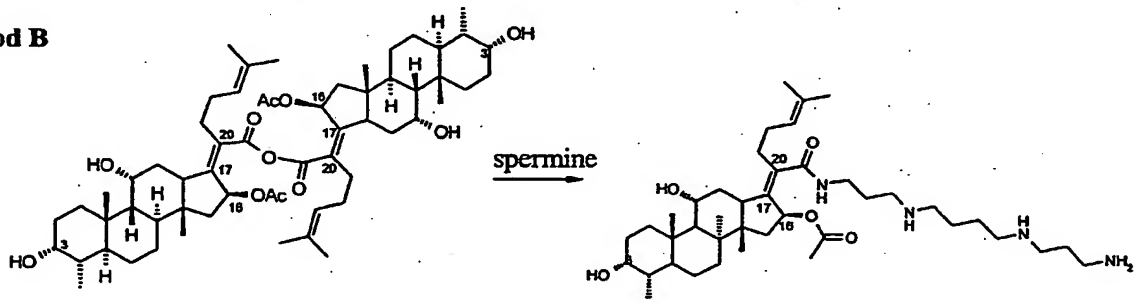
Alternative preparation of compounds in which the polyamine is linked to C-21 of fusidic acid by an amide bond

Alternatively, the compounds of the invention can be prepared by reacting anhydrides of fusidic acid derivatives, e.g. fusidic acid anhydride in scheme 2, with excess of the branched polyamine building blocks (Scheme 2).

Preparation of Compound 107 using general method B, Scheme 2

The method is illustrated by an example in Scheme 2 where the fusidic acid nucleus is represented by natural fusidic acid. Fusidic acid (1 eauivalent) is dissolved in anhydrous DMF and and N,N-dicyclohexylcarbodiimide (2.2 equivalents) was added. The resulting reaction mixture was heated at 50 °C for 24 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. Pure anhydride is obtained either by crystallisation from hot methanol or by chromatography on silica gel using mixtures of ethyl acetate and petroleum ether as eluant. Spermine (3 equivalents) in anhydrous chloroform under argon is then slowly added over a period of 30 min to a chloroform solution containing fusidic acid anhydride. The reaction mixture is stirred at room temperature for 16 h after which time chloroform is evaporated under reduced pressure resulting a pale yellow oil. Pure Compound 107 is obtained after chromatography on silica gel using a mixture of dichloromethan, methanol and 25% aqueaous ammonia as eluant. A white powder of pure Compound 107 is obtained after freeze drying of purified product in yields ranging from 70-90%.

Method B



Fusidic acid anhydride

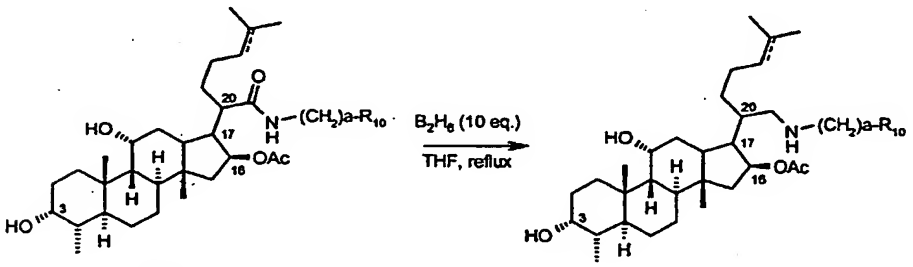
Compound 107

Scheme 2. General example for the preparation of compounds of the invention using method B.

Reduction of the amide bond

The amide bonding resulting from the reaction of a polyamine and a succinimide ester or carboxylic acid anhydride described in scheme 1 and 2 respectively (e.g. compounds of Compound 125 and 107) can be reduced to the corresponding amine by reacting the amide with a 10 fold excess of diborane in refluxing THF for 5-10 hours, as depicted in scheme 3. The reaction mixture is

subsequently acidified with 4N aqueous hydrochloric acid to pH 1 and stirred vigorously for 2-4 hours. The reaction mixture is then freeze dried and the resulting white powder is purified on silica gel using a mixture of dichloromethan, methanol and 25% aqueaous ammonia as eluant. A white powder is obtained after freeze drying of purified product.



IV VII

Scheme 3. Preparation of C-21 polyaminated fusidic acid analogues of formula IV.

Introduction of polyamines by reductive amination of ketones

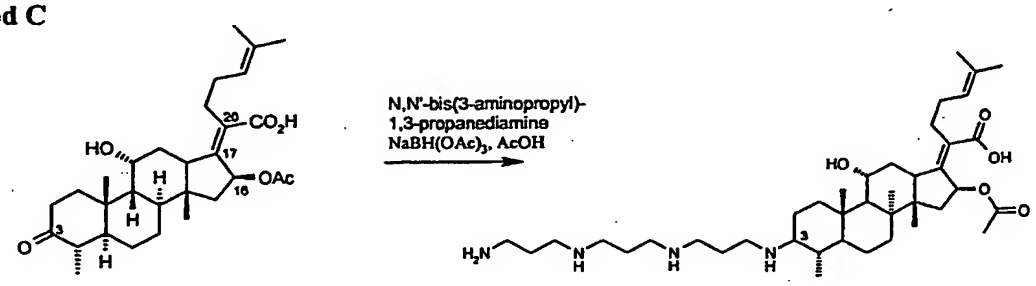
Compounds of the invention where the polyamine moiety is linked to various sites of the fusidic acid nucleus can be prepared from steroid analogues containing a keto or aldehyde functionality where substitution with the branched polyamine is desired. The appropriate fusidic acid having an aldehyde or a keto functionality can be obtained from various known derivatives of fusidic acid by methods known to those skilled in the art (e.g. oxidation method of hydroxy groups, allylic oxidation and partial reduction of carboxylic esters, etc.). For example 3- or 16-keto derivatives of fusidic acid can be reacted directly with the unprotected polyamine building block by means of reductive amination using methods reported for the preparation of synthetic squalamines (Pechulis *et al.*, 1995; Weis *et al.*, 1999; Kinney *et al.*, 2000).

Preparation of Compound 113 using general method C, Scheme 4

The method is illustrated by an example in Scheme 4 where the fusidic acid nucleus is represented by 3-keto fusidic acid. Fusidic acid is first oxidised to 3-keto fusidic acid by means of CrO_3, altenatively by pyridinium dichromate, Dess-Martin periodinane or by a Swern protocol. To a solution of 3-keto fusidic acid (1 equivalent) in methanol was added successively N,N'-bis(3-aminopropyl)-1,3-propanediamine (3 equivalents), acetic acid and $NaBH(OAc)_3$ (3 equivalents) and the resultin reaction mixture was stirred for 6-16 h, after which time methanol is evaporated under reduced pressure providing a pale yellow oil. Pure Compound 113 is obtained after chromatography on silica gel using a mixture of dichloromethan, methanol and 25% aqueaous ammonia as eluant. A

white powder of pure Compound 113 is obtained after freeze drying of purified product in yields ranging from 70-85%.

Method C



3-ketofusidic acid

Compound 113

Scheme 4. Representative example for the introduction of branched polyamine fragments to a steroid nucleus containing a carbonyl function via reductive amination using $NaBH(OAc)_3$ as reducing agent (Abdel-Magid, 1996).

Sulfation of free hydroxy groups:

All compounds of the invention containing one or several free hydroxy groups can optionally be sulfated either selectively at one hydroxy group or at several hydroxy group using stoichiometric or excess amounts of sulfur trioxide-pyridine complex, respectively as reported in the litterature (Kinney *et al.*, 2000). Sulfatation is carried out prior to coupling reactions A, B and C.

Acetylation of hydroxy groups

Acetylation of the free hydroxy groups of fusidic acid derivatives is carried out using an excess of acetic acid anhydride in pyridine at room temperature under anhydrous conditions.

Reduction of double bonds

Double bonds of fusidic acid derivatives are carried out by means of catalytic hydrogenation using palladium on carbon as catalyst and acetic acid as solvent. The reactions are shaken for 6-20 h at room temperature.

Dehydration of 11-OH

Dehydration of 11-OH of fusidic acid derivatives is achieved by trating fusidic acid derivatives by excess thionyl chloride in pyridine and dichloromethan at 0°C under anhydrous conditions.

Removal of the 16-acetoxy group

The 16-acetoxy group of fusidic acid derivatives can be removed by reacting the corresponding methyl ester in refluxing anhydrous methanol in presence of excess magnesium turnings under anhydrous conditions. The methyl ester is then removed by refluxing in aqueous sodium hydroxide for 1 h.

Purification of the compounds of the invention:

The resulting compounds of the invention can be purified by column chromatography on silca gel 60 (E. Merck), 230-400 mesh using mixtures of dichloromethan, methanol and aqueous ammonia as eluant. Alternatively, the compounds of the invention can be purified by reversed phase preparative high performance liquid chromatography (HPLC) using acetonitrile buffered with trifluoroacetic acid or acetic acid as eluant.

Oxidation of hydroxy groups

Keto derivatives can be obtained by oxidation of the corresponding hydroxy group of a fusidic acid derivative by various methods such as CrO_3 in DMF or dichloromethan, pyridinium dichromate, pyridinium chlorochromateDess-Martin periodinane by a Swern protocol or by using radical reagent such as TEMPO.

Preparation of N-succinimide esters of fusidic acid analogues, general method D:

The fusidic acid derivative (1 equivalent) was dissolved in anhydrous THF. To the solution was added successively N-hydroxysuccinimide (1.1 eauivalent) and N,N-dicyclohexylcarbodiimide (1.2 equivalent). The resulting reaction mixture was stirred at room temperature for 20 hours. The reaction was filtered, the filtrate was concentrated under reduced pressure and redissolved in ethyl acetate. The organic solution was washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Pure N-succinimide esters were obtained either by crystallisation from hot methanol or by chromatography on silica gel using mixtures of ethyl acetate and petroleum ether as eluant.

Preparation of anhydrides of fusidic acid analogues, general method E:

The fusidic acid derivative was dissolved in anhydrous DMF and and N,N-dicyclohexylcarbodiimide (2.2 equivalents) was added. The resulting reaction mixture was heated at 50 °C for 24 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. Pure anhydride was obtained either by crystallisation from hot methanol or by chromatography on silica gel using mixtures of ethyl acetate and petroleum ether as eluant.

Preparation 1: Fusidic anhydride, Compound 1

The title compound was prepared from fusidic acid according to general method E.

^{13}C NMR ($CDCl_3$): 171.0, 164.7, 153.2, 132.6, 129.1, 123.0, 74.2, 71.4, 68.3, 49.2, 48.8, 44.7, 39.5, 39.1, 37.0, 36.2, 36.1, 35.5, 32.3, 30.3, 30.0, 29.0, 28.9, 25.8, 24.2, 22.8, 21.1, 20.8, 18.0, 17.9, 15.9

Preparation 2: 3β-Hydroxy-17R,20S,24,25-tetrahydrofusidic acid succinimide ester, Compound 2

The title compound was prepared from 3β-hydroxy-17R,20S,24,25-tetrahydrofusidic acid according to method D.

^{13}C NMR ($CDCl_3$): 171.1, 170.6, 169.8, 168.7, 79.3, 67.9, 49.7, 49.6, 49.1, 46.9, 42.7, 40.4, 40.1, 40.0,
39.9, 38.7, 36.6, 35.4, 34.1, 32.6, 32.2, 31.8, 27.9, 25.8, 25.5, 25.0, 24.6, 23.9, 23.3, 22.5, 21.3, 21.3, 16.7, 15.4

Preparation 3: 17R,20S,24,25-Tetrahydrofusidic acid succinimide ester, Compound 3

The title compound was prepared from 17R,20S,24,25-tetrahydrofusidic acid according to method D.

^{13}C NMR ($CDCl_3$): 171.1, 170.6, 169.8, 168.8, 79.0, 71.6, 67.9, 49.8, 49.5, 49.0, 46.6, 40.3, 40.2, 40.0,
38.7, 37.0, 36.5, 36.3, 35.2, 32.4, 31.9, 30.1, 30.0, 28.0, 25.7, 24.6, 23.4, 22.9, 22.5, 22.5, 21.3, 21.1, 16.8, 16.0

Preparation 4: 17S,20R-Dihydrofusidic acid succinimide ester, Compound 4

The title compound was prepared from 17S,20R-dihydrofusidic acid according to method D.

^{13}C NMR ($CDCl_3$): 171.3, 170.1, 169.2, 132.5, 123.1, 114.0, 75.9, 71.5, 68.6, 49.3, 44.1, 43.4, 41.2, 40.6, 39.1, 37.2, 36.5, 36.1, 34.5, 34.0, 33.3, 32.7, 30.2, 30.1, 25.7, 25.6, 25.3, 23.9, 22.4, 21.4, 20.9, 18.3, 17.7, 16.0

Preparation 5: 11-Desoxy-17R,20S,24,25-tetrahydrofusidic acid succinimide ester, Compound 5
The title compound was prepared from 11-desoxy-17R,20S,24,25-tetrahydrofusidic acid according to method D.
^{13}C NMR ($CDCl_3$):170.8, 170.6, 168.9, 77.4, 71.8, 49.2, 49.0, 45.0, 44.5, 44.2, 39.9, 39.4, 38.7, 37.8, 36.4, 34.9, 33.4, 30.6, 30.0, 28.6, 27.9, 25.6, 25.1, 25.0, 22.9, 22.6, 22.5, 21.3, 20.2, 20.2, 17.4, 16.0

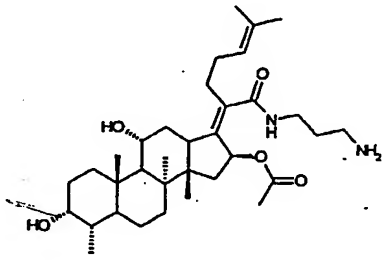
Preparation 6: 17R,20R,S,24,25-Tetrahydro-16-desoxyfusidic acid succinimide ester, Compound 6
The title compounds was prepared from two separate C-20 epimers of 17R,20,24,25-tetrahydro-16-desoxyfusidic acid according to method D.
^{13}C NMR ($CDCl_3$):
C-20 epimer-1: 170.6, 169.9, 168.9, 71.6, 68.5, 51.0, 49.9, 43.8, 42.7, 40.2, 38.7, 37.0, 36.9, 36.1, 34.4, 32.4, 32.0, 30.5, 30.1, 29.9, 27.8, 25.6, 25.4, 23.3, 22.7, 22.6, 22.5, 21.4, 16.0, 15.6
C-20 epimer-2: 172.1, 170.0, 168.9, 71.7, 68.1, 51.0, 50.1, 48.8, 42.6, 40.9, 40.3, 38.8, 37.1, 36.4, 35.7, 32.9, 32.5, 30.8, 30.2, 30.0, 28.2, 27.9, 25.7, 25.6, 24.8, 23.4, 22.8, 22.6, 22.5, 21.1, 16.1

Preparation 7: 13(17)-en-17R,20,24,25-Tetrahydrofusidic acid succinimide ester, Compound 7
The title compound was prepared from 13(17)-en-17R,20,24,25-tetrahydrofusidic acid according to method 2.
^{13}C NMR ($CDCl_3$): 169.1, 168.7, 143.2, 130.5, 71.5, 69.9, 57.7, 55.8, 51.4, 41.6, 41.3, 38.4, 37.7, 36.8,
35.1, 34.2, 30.6, 30.4, 29.8, 29.8, 29.4, 29.3, 27.8, 25.6, 24.6, 24.2, 23.2, 22.7, 22.6, 22.5, 21.7, 15.9

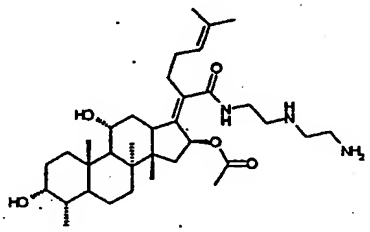
Preparation 8: 16(17)-en-17R,20R,S,24,25-Tetrahydrofusidic acid succinimide ester, Compound 8
The title compound was prepared from 16(17)-en-17R,20,24,25-tetrahydrofusidic acid according to method D.
NMR ($CDCl_3$) (*1:1 mixture of C-20 epimers)*: 169.3, 169.2, 169.1, 140.3, 140.2, 128.4, 127.1, 77.2, 71.7, 71.6, 68.7, 68.6, 54.1, 53.8, 50.6, 50.5, 49.2, 44.1, 43.5, 43.1, 42.7, 40.1, 40.1, 39.0, 38.9, 38.6, 38.6, 37.4, 36.6, 36.6, 36.2, 34.0, 32.7, 32.6, 32.5, 31.9, 30.6, 30.4, 30.3, 30.2, 30.2, 30.2, 27.8, 25.6,

25.3, 25.2, 25.1, 25.0, 25.0, 22.6, 22.5, 20.9, 17.6, 17.6, 16.1

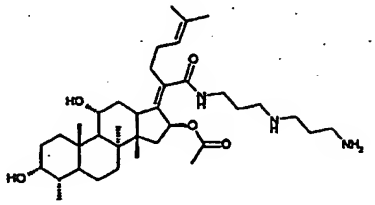
Examples of compounds of the inventions prepared by method A, B or C:

Example no./Comp. no.	Method	Steroid starting material	Polyamine starting material	Structure of compound
1/101	B	Fusidic acid anhydride	1,3-diamino-propane	

^{13}C NMR (CD_3OD), δ/ppm: 174.5, 172.4, 143.4, 135.8, 133.2, 124.5, 75.2, 72.4, 68.6, 50.7, 44.6, 40.7, 40.3, 39.9, 38.2, 37.9, 37.9, 37.4, 36.9, 32.9, 31.1, 31.0, 30.5, 28.8, 25.9, 23.9, 23.8, 22.4, 21.2, 17.9, 17.9, 16.5

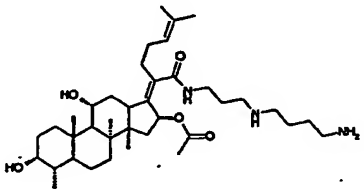
2/102	B	Fusidic acid anhydride	diethylenetriamine	

NMR (CD_3OD), δ/ppm: 174.6, 172.4, 143.4, 135.7, 133.2, 124.5, 75.2, 72.4, 68.6, 51.4, 50.7, 44.6, 41.5, 40.7, 40.3, 40.2, 38.2, 37.8, 37.4, 36.8, 32.9, 31.0, 31.0, 30.5, 28.8, 25.9, 23.8, 22.4, 21.2, 17.9, 17.9, 16.5

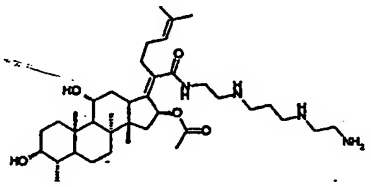
3/103	B	Fusidic acid anhydride	3,3'-diamino-dipropylamine	

^{13}C NMR (CD_3OD), δ/ppm: 171.2, 171.1, 140.8, 135.9, 132.2, 123.5, 73.4, 71.4, 68.2, 49.5, 49.2, 48.4, 47.8, 43.2, 40.6, 39.6, 39.5, 39.3, 37.0, 36.4, 36.0, 35.6, 34.1, 32.3, 30.2, 30.0, 29.2, 28.0, 27.8,

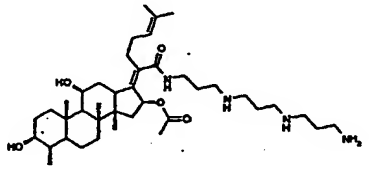
25.8, 23.9, 23.0, 21.1, 20.9, 17.9, 17.6, 16.0

4/104	B	Fusidic acid anhydride	spermidine	

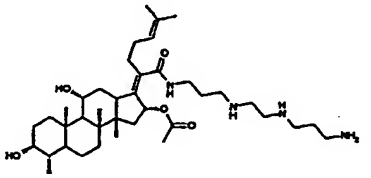
^{13}C NMR (CD_3OD), δ/ppm: 174.5, 172.4, 143.5, 135.7, 133.2, 124.5, 75.2, 72.4, 68.6, 50.7, 50.3, 50.1, 48.3, 47.9, 44.6, 42.0, 40.7, 40.3, 38.5, 38.2, 37.9, 37.4, 36.9, 32.9, 31.1, 31.0, 30.5, 30.5, 28.9, 27.8, 25.9, 23.9, 23.8, 22.4, 21.2, 17.9, 16.5

5/105	B	Fusidic acid anhydride	N,N'-bis(2-aminoethyl)-1,3-propanediamine	

^{13}C NMR (CD_3OD), d/ppm: 174.6, 172.4, 143.5, 135.7, 133.3, 124.5, 75.2, 72.5, 68.6, 52.4, 50.7, 48.6, 44.6, 41.6, 40.7, 40.3, 40.1, 38.2, 37.9, 37.4, 36.9, 32.9, 31.0, 30.5, 30.4, 28.8, 25.9, 23.9, 23.8, 22.4, 21.2, 18.0, 17.9, 16.5

6/106	B	Fusidic acid anhydride	N,N'-bis(3-aminopropyl)-1,3-propanediamine	

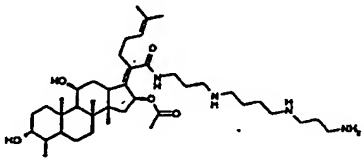
^{13}C NMR (CD_3OD), δ/ppm: 171.1, 140.7, 136.0, 132.1, 123.6, 73.5, 71.4, 68.0, 50.6, 49.4, 49.2, 48.5, 48.4, 48.3, 48.0, 43.2, 40.4, 39.8, 39.5, 39.3, 36.9, 36.5, 36.0, 35.8, 33.3, 32.2, 30.7, 30.1, 30.0, 29.3, 28.1, 27.8, 25.8, 23.9, 23.0, 21.1, 20.9, 17.9, 17.6, 16.0

7/107	B	Fusidic acid anhydride	N,N'-bis(3-aminopropyl)-ethylenediamine	

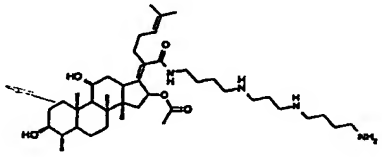
^{13}C NMR (CD_3OD), δ/ppm: 174.4, 172.4, 143.4, 135.8, 133.2, 124.5, 75.2, 72.4, 68.6, 50.7, 50.5, 48.0, 44.6, 40.7, 40.6, 40.3, 38.5, 38.2, 37.9, 37.4, 36.9, 32.9, 32.8, 31.1, 31.0, 30.5, 29.9, 28.9, 28.3, 28.2,

25.9, 23.9, 23.8, 22.4, 21.2, 18.0, 17.9, 16.5

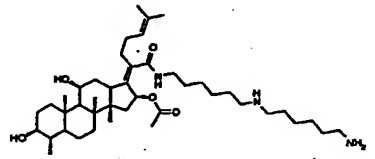
MS (direct inlet) m/z = 701.55 $(M+H)^+$, 321.48, 203.21, 89.06

8/108	B	Fusidic acid anhydride	spermine	

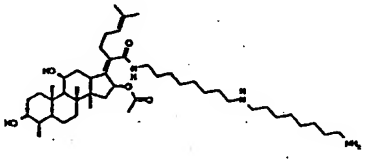
^{13}C NMR (CD_3OD), δ/ppm: 178.7, 72.5, 69.3, 54.1, 51.8, 51.7, 48.1, 43.8, 42.4, 41.5, 40.6, 40.2, 38.3, 38.2, 38.0, 37.1, 36.8, 33.1, 32.7, 32.6, 31.7, 31.2, 31.1, 30.1, 29.2, 28.6, 26.6, 23.8, 23.2, 22.9, 22.7, 16.6, 16.4

9/109	B	Fusidic acid anhydride	N,N'-bis(4-aminobutyl)-1,3-propanediamine	

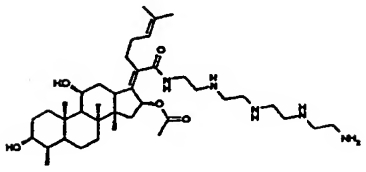
^{13}C NMR (CD_3OD), δ/ppm: 174.3, 172.4, 143.2, 135.9, 133.2, 124.6, 75.3, 72.4, 68.6, 50.7, 50.1, 48.6, 44.5, 41.9, 40.7, 40.4, 40.3, 38.2, 37.9, 37.4, 36.9, 32.9, 31.1, 31.0, 30.5, 30.4, 29.5, 28.8, 28.0, 27.8, 27.6, 25.9, 23.9, 23.8, 22.4, 21.2, 18.0, 17.9, 16.5

10/110	B	Fusidic acid anhydride	6,6'-diamino-dihexylamine	

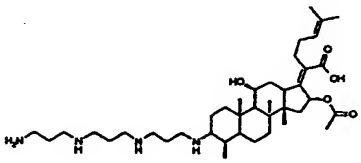
^{13}C NMR (CD_3OD), δ/ppm: 174.3, 172.4, 143.1, 135.8, 133.2, 124.6, 75.3, 72.5, 68.6, 50.7, 50.6, 50.6, 44.5, 42.4, 40.7, 40.6, 40.3, 38.2, 37.9, 37.4, 36.9, 33.4, 32.9, 31.1, 30.5, 30.3, 30.2, 28.8, 28.3, 28.1, 28.1, 27.9, 25.9, 23.9, 22.4, 21.2, 18.0, 17.9, 16.5

11/111	A	Fusidic acid anhydride	8,8'-diamino-dioctylamine	

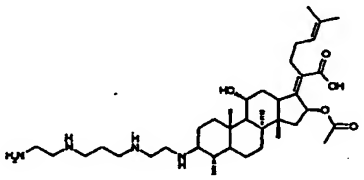
^{13}C NMR (CD_3OD), δ/ppm: 174.3, 172.4, 143.1, 135.8, 133.1, 124.6, 75.3, 72.5, 68.6, 50.7, 44.5, 42.5, 40.7, 40.6, 40.3, 38.2, 37.9, 37.4, 36.9, 33.6, 32.9, 31.1, 30.6, 30.6, 30.4, 30.3, 28.8, 28.4, 28.4, 28.1, 28.0, 25.9, 23.8, 22.4, 21.2, 18.0, 17.9, 16.5

12/112	B	Fusidic acid anhydride	tetraethylene-pentamine	

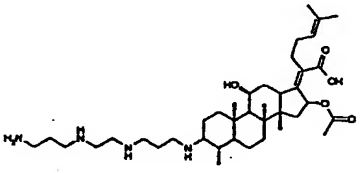
^{13}C NMR (CD_3OD), δ/ppm: 171.5, 171.1, 141.0, 135.5, 132.1, 123.6, 73.9, 71.3, 68.1, 51.3, 49.4, 48.9, 48.6, 48.2, 43.2, 41.2, 39.5, 39.3, 38.9, 36.9, 36.5, 36.0, 35.7, 32.2, 30.2, 30.0, 29.5, 28.1, 25.8, 24.0, 23.1, 21.2, 20.9, 17.9, 17.7, 16.0

13/113	C	Fusidic acid anhydride	N,N'-bis(3-aminopropyl)-1,3-propanediamine	

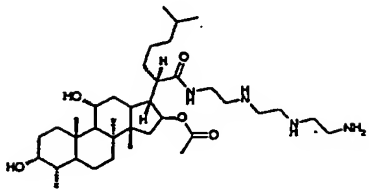
^{13}C NMR (CD_3OD), δ/ppm: 179.5, 173.4, 139.9, 137.5, 132.3, 125.6, 75.9, 68.9, 61.1, 50.8, 43.6, 40.8, 40.3, 40.2, 37.7, 37.6, 37.3, 31.9, 31.1, 30.9, 30.7, 29.3, 28.9, 27.5, 25.9, 25.4, 24.6, 23.7, 22.6, 21.2, 18.0, 17.7, 16.7

14/114	C	Fusidic acid anhydride	N,N'-bis(2-aminoethyl)-1,3-propanediamine	

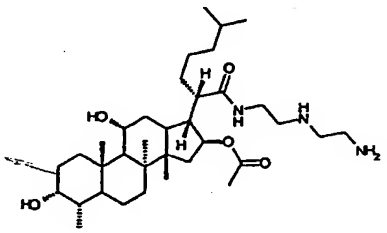
^{13}C NMR (CD_3OD), δ/ppm: 180.3, 179.5, 173.2, 139.4, 138.3, 132.4, 125.5, 75.9, 68.9, 60.4, 50.8, 50.0, 49.9, 48.1, 47.9, 47.6, 45.5, 43.7, 40.8, 40.3, 40.1, 37.7, 37.5, 37.4, 31.9, 31.0, 29.3, 27.9, 26.0, 24.6, 24.2, 23.5, 22.7, 21.3, 18.0, 17.7, 16.7

15/115	C	Fusidic acid anhydride	N,N'-bis(3-aminopropyl)-ethylenediamine	

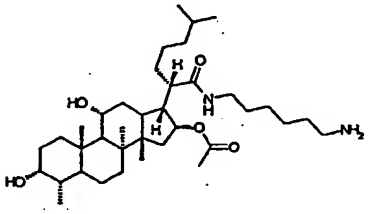
^{13}C NMR (CD_3OD), δ/ppm: 179.6, 173.3, 139.7, 137.6, 132.3, 125.6, 75.9, 68.9, 61.0, 50.8, 50.0, 49.9, 48.6, 43.6, 40.8, 40.3, 40.1, 37.6, 37.6, 37.4, 37.2, 31.8, 31.1, 30.5, 30.5, 29.2, 27.6, 25.9, 25.1, 24.7, 23.5, 22.7, 21.2, 18.0, 17.6, 16.6

16/116	A	Tetrahydrofusidic acid- *N*-succinimide ester	tetraethylene-tetramine	

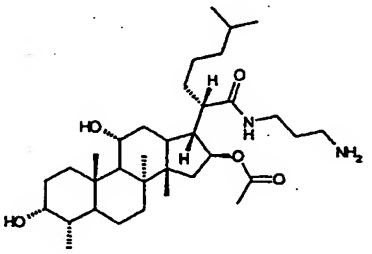
^{13}C NMR (CD_3OD), δ/ppm: 177.8, 172.6, 80.5, 72.5, 68.9, 51.9, 51.3, 50.4, 50.1, 41.7, 41.4, 41.1, 40.1, 40.1, 38.3, 38.0, 37.0, 36.5, 33.0, 32.0, 31.1, 29.1, 26.3, 23.9, 23.4, 23.1, 22.9, 22.6, 21.4, 17.1, 16.5

17/117	A	Tetrahydrofusidic acid- *N*-succinimide ester	diethylenetriamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.8, 172.6, 80.5, 72.5, 68.9, 51.9, 51.5, 51.3, 50.4, 50.1, 41.7, 41.5, 41.4, 41.1, 40.2, 40.1, 38.3, 38.0, 37.1, 36.5, 33.1, 32.0, 31.1, 29.1, 26.3, 23.9, 23.4, 23.1, 22.9, 22.6, 21.4, 17.1, 16.5

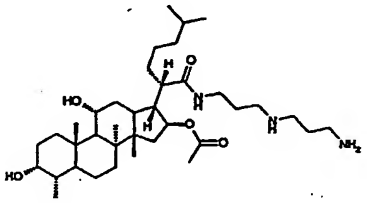
18/118	C	Tetrahydrofusidic acid- *N*-succinimide ester	1,6-hexanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.4, 172.6, 80.1, 72.5, 69.0, 51.4, 51.3, 50.3, 50.1, 42.3, 41.6, 41.4, 41.1, 40.3, 40.1, 38.3, 37.9, 37.0, 36.3, 33.2, 33.1, 31.7, 31.0, 30.3, 29.2, 28.0, 27.7, 26.4, 23.9, 23.3, 23.1, 23.0, 22.6, 21.4, 17.1, 16.5

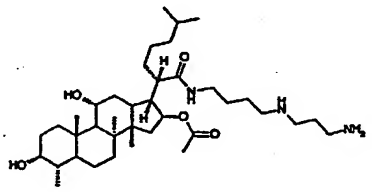
19/119	A	Tetrahydrofusidic acid- *N*-succinimide ester	1,3-diamino-propane	

NMR (CD_3OD), δ/ppm: 177.7, 172.6, 80.2, 72.5, 68.9, 51.5, 51.3, 50.3, 50.1, 41.6, 41.4, 41.1, 40.1,

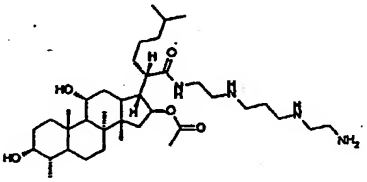
39.9,
38.3, 38.0, 37.7, 37.1, 36.4, 33.1, 32.8, 31.7, 31.1, 29.1, 26.4, 23.9, 23.3, 23.1, 22.9, 22.6, 21.4, 17.1, 16.5

20/120	A	Tetrahydrofusidic acid- *N*-succinimide ester	3,3'-diamino-dipropylamine	

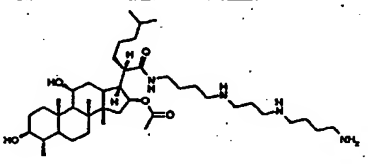
^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 80.2, 72.5, 68.9, 51.6, 51.3, 50.4, 50.1, 48.4, 41.6, 41.4, 41.1, 40.6, 40.1, 38.3, 38.0, 37.1, 36.4, 33.1, 32.6, 31.8, 31.1, 30.1, 29.2, 26.4, 23.9, 23.3, 23.2, 23.0, 22.6, 21.4, 17.1, 16.5

21/121	A	Tetrahydrofusidic acid- *N*-succinimide ester	spermidine	

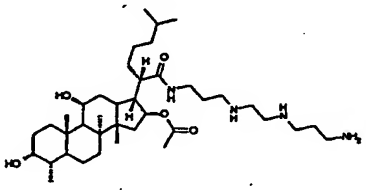
^{13}C NMR (CD_3OD), δ/ppm: 177.7, 172.6, 80.2, 72.5, 68.9, 51.5, 51.3, 50.3, 50.2, 50.1, 47.8, 41.5, 41.4, 41.1, 40.1, 38.3, 38.1, 38.0, 37.1, 36.4, 33.1, 31.8, 31.1, 29.8, 29.4, 29.2, 27.5, 26.4, 23.9, 23.3, 23.2, 23.0, 22.6, 21.4, 17.1, 16.5

22/122	A	Tetrahydrofusidic acid- *N*-succinimide ester	N,N'-bis(2-aminoethyl)-1,3-propanediamine	

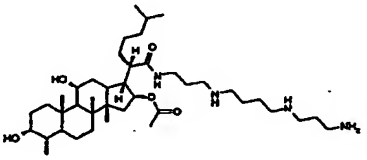
^{13}C NMR (CD_3OD), δ/ppm: 177.8, 172.5, 80.3, 72.4, 69.0, 51.7, 51.3, 50.7, 50.4, 50.1, 41.6, 41.4, 41.1, 40.8, 40.1, 39.9, 38.3, 37.9, 37.0, 36.4, 33.0, 31.9, 31.1, 29.8, 29.1, 26.3, 23.9, 23.3, 23.1, 22.9, 22.6, 21.4, 17.1, 16.5

23/123	A	Tetrahydrofusidic acid- *N*-succinimide ester	N,N'-bis(4-aminobutyl)-1,3-propanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 80.1, 72.5, 69.0, 51.4, 51.3, 50.3, 50.1, 48.0, 41.6, 41.4, 41.1, 40.8, 40.1, 40.0, 38.3, 37.9, 37.0, 36.3, 33.0, 31.8, 31.1, 29.1, 27.8, 27.8, 26.7, 26.6, 26.3, 23.9, 23.3, 23.1, 23.0, 22.6, 21.4, 17.0, 16.5

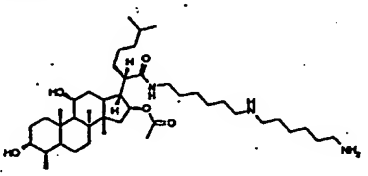
24/124	A	Tetrahydrofusidic acid- *N*-succinimide ester	N,N'-bis(3-aminopropyl)-ethylenediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 80.2, 72.4, 68.9, 51.5, 51.3, 50.3, 50.1, 48.3, 41.6, 41.3, 41.1, 40.5, 40.1, 38.3, 37.9, 37.1, 36.4, 33.1, 32.4, 31.8, 31.1, 30.3, 29.2, 26.4, 23.9, 23.3, 23.2, 23.0, 22.6, 21.4, 17.1, 16.5

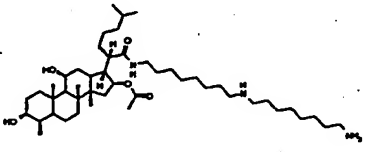
25/125	A	Tetrahydrofusidic acid- *N*-succinimide ester	

^{13}C NMR (CD_3OD), δ/ppm: ^{13}C NMR: (CD_3OD)177.6, 172.5, 80.2, 72.4, 68.9, 51.5, 51.2, 50.3, 50.1, 48.1, 47.9, 41.5, 41.3, 41.1, 40.4, 40.1, 38.3, 38.1, 37.9, 37.0, 36.4, 33.0, 31.8, 31.3, 31.0, 29.8, 29.1, 28.0, 27.8, 26.4, 23.9, 23.3, 23.2, 23.0, 22.6, 21.4, 17.1, 16.5

MS (direct inlet) m/z = 705.59 $(M+H)^+$, 604.70, 344.44, 305.42, 225.20, 203.21

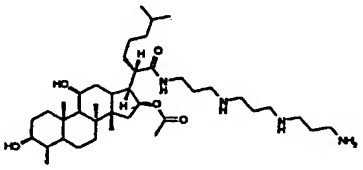
26/126	A	Tetrahydrofusidic acid- *N*-succinimide ester	6,6'-diamino-dihexylamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.4, 172.6, 80.1, 72.5, 69.0, 51.4, 51.3, 50.7, 50.3, 50.1, 42.4, 41.6, 41.4, 41.1, 40.3, 40.1, 38.3, 37.9, 37.0, 36.3, 33.3, 33.1, 31.7, 31.0, 30.3, 29.2, 28.3, 28.2, 28.1, 27.9, 26.4, 23.9, 23.3, 23.1, 23.0, 22.6, 21.4, 17.1, 16.5

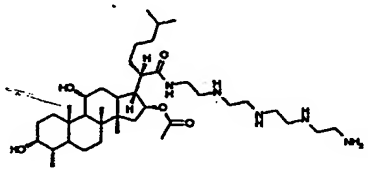
27/127	A	Tetrahydrofusidic acid- *N*-succinimide ester	8,8'-diamino-dioctylamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.3, 172.6, 80.1, 72.5, 69.0, 51.4, 51.3, 50.7, 50.3, 50.1, 42.4, 41.5, 41.4, 41.1, 40.3, 40.1, 38.3, 37.9, 37.0, 36.3, 33.3, 33.1, 31.7, 31.0, 30.6, 30.6, 30.5, 30.4, 30.3, 30.3,

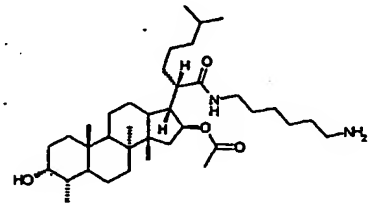
29.2, 28.4, 28.2, 28.0, 26.4, 23.9, 23.3, 23.2, 23.0, 22.6, 21.4, 17.1, 16.5

28/128	A	Tetrahydrofusidic acid- *N*-succinimide ester	N,N'-bis(3-aminopropyl)-1,3-propanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.8, 172.6, 80.1, 72.5, 68.9, 51.3, 50.3, 50.1, 47.7, 47.6, 41.5, 41.4, 41.1, 40.1, 39.9, 38.3, 38.0, 37.0, 36.4, 33.1, 31.8, 31.1, 29.1, 29.0, 29.0, 28.0, 26.4, 23.9, 23.3, 23.2, 23.0, 22.6, 21.4, 17.1, 16.5

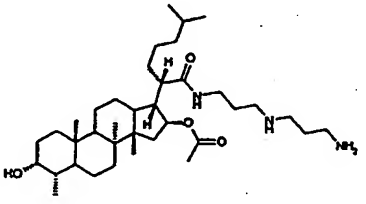
29/129	A	Tetrahydrofusidic acid- *N*-succinimide ester	tetraethylene-pentamine	

^{13}C NMR (CD_3OD), δ/ppm: 178.2, 173.0, 80.9, 72.9, 69.3, 52.3, 51.7, 51.5, 50.8, 50.5, 48.4, 42.1, 41.8, 41.7, 41.5, 40.5, 40.5, 38.7, 38.4, 37.5, 36.9, 33.5, 32.4, 31.5, 29.5, 26.7, 24.3, 23.8, 23.6, 23.3, 23.0, 21.8, 17.6, 16.9

30/130	A	11-desoxy-tetrahydro fusidic acid *N*-succinimide ester	1,6-hexanediamine	

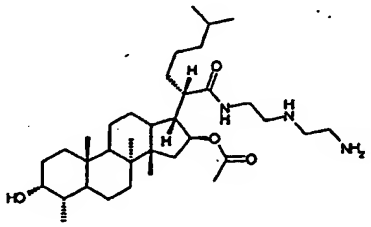
NMR (CD_3OD), δ/ppm: 177.3, 172.6, 80.7, 72.4, 52.1, 50.8, 50.6, 46.6, 45.9, 42.4, 41.0, 40.4, 40.3, 40.0,

38.9, 37.4, 36.4, 34.4, 33.4, 32.2, 31.1, 30.3, 30.0, 29.1, 28.1, 27.8, 26.8, 26.3, 24.5, 23.1, 22.9, 21.6, 21.3, 21.3, 20.7, 17.8, 16.5

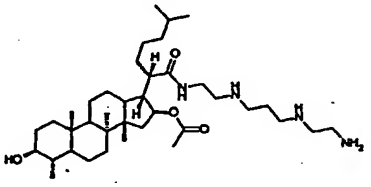
31/131	A	11-desoxy-tetrahydro fusidic acid *N*-succinimide ester	3,3'-diamino-dipropylamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 80.5, 72.4, 52.0, 50.9, 50.5, 46.6, 45.9, 41.0, 40.6, 40.4,

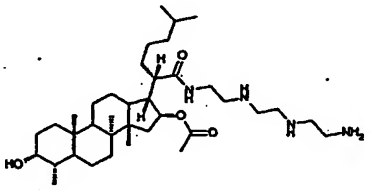
40.0, 39.0, 38.3, 37.4, 36.3, 34.5, 33.0, 32.1, 31.1, 30.1, 30.0, 29.1, 26.8, 26.4, 24.5, 23.1, 22.9, 21.6, 21.3, 21.3, 20.7, 17.8, 16.5

32/132	A	11-desoxy-tetrahydro fusidic acid *N*-succinimide ester	diethylenetriamine	

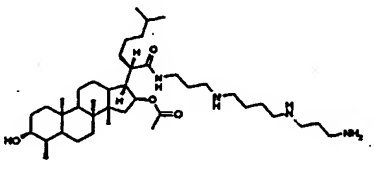
^{13}C NMR (CD_3OD), δ/ppm: 177.6, 172.6, 80.4, 72.5, 52.0, 51.9, 50.9, 50.5, 46.5, 45.9, 41.8, 41.0, 40.4, 40.0, 39.0, 37.4, 36.4, 34.5, 32.0, 31.1, 29.9, 29.1, 26.8, 26.3, 24.4, 23.1, 22.9, 21.6, 21.3, 21.3, 20.7, 17.8, 16.5

33/133	A	11-desoxy-tetrahydro fusidic acid *N*-succinimide ester	N,N'-bis(2-aminoethyl)-1,3-propanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.7, 172.6, 80.4, 72.4, 52.4, 51.9, 50.8, 50.5, 49.8, 48.7, 48.6, 46.6, 45.9, 41.6, 41.0, 40.4, 40.0, 39.9, 39.0, 37.4, 36.4, 34.5, 32.1, 31.1, 30.5, 30.0, 29.1, 26.8, 26.3, 24.5, 23.1, 22.9, 21.6, 21.3, 21.3, 20.7, 17.8, 16.5

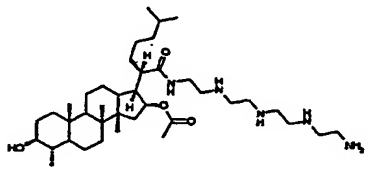
34/134	A	11-desoxy-tetrahydro fusidic acid *N*-succinimide ester	tetraethylene-tetramine	

^{13}C NMR (CD_3OD), δ/ppm: 177.6, 172.6, 80.4, 72.4, 52.4, 51.9, 50.8, 50.5, 46.5, 45.9, 41.8, 41.0, 40.4, 40.0, 38.9, 37.4, 36.3, 34.5, 32.0, 31.1, 30.0, 29.1, 26.8, 26.3, 24.4, 23.1, 22.9, 21.6, 21.3, 21.3, 20.7, 17.8, 16.5

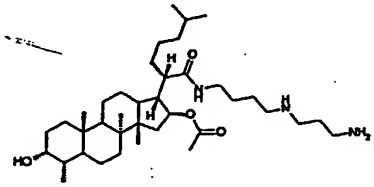
35/135	A	11-desoxy-tetrahydro fusidic acid *N*-succinimide ester	spermine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 80.5, 72.4, 52.0, 50.8, 50.6, 50.5, 50.5, 46.6, 45.9, 41.0,

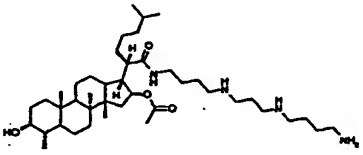
40.6, 40.4, 40.0, 38.9, 38.3, 37.4, 36.3, 34.5, 32.7, 32.1, 31.1, 30.1, 30.0, 29.1, 28.3, 28.2, 26.8, 26.4, 24.4, 23.1, 22.9, 21.6, 21.3, 21.3, 20.7, 17.8, 16.5

36/136	A	11-desoxy-tetrahydro fusidic acid *N*-succinimide ester	tetraethylene-pentamine	

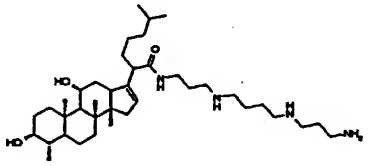
^{13}C NMR (CD_3OD), δ/ppm: 178.1, 173.0, 80.8, 72.8, 52.3, 51.2, 50.9, 46.9, 46.3, 41.4, 40.8, 40.4, 39.4, 37.8, 36.8, 34.9, 32.5, 31.5, 30.4, 29.5, 27.2, 26.7, 24.9, 23.5, 23.3, 22.0, 21.8, 21.7, 21.1, 18.2, 16.9

37/137	A	11-desoxy-tetrahydro fusidic acid *N*-succinimide ester	spermidine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 80.6, 72.4, 52.0, 50.9, 50.6, 50.5, 46.6, 45.9, 42.3, 41.0, 40.4, 40.0, 39.0, 38.3, 37.4, 36.3, 34.5, 32.1, 31.3, 31.1, 30.1, 30.0, 29.1, 27.9, 26.8, 26.4, 24.5, 23.1, 22.9, 21.6, 21.3, 21.3, 20.7, 17.8, 16.5

38/138	A	11-desoxy-tetrahydro fusidic acid *N*-succinimide ester	N,N'-bis(4-aminobutyl)-1,3-propanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.1, 172.3, 80.3, 72.2, 51.7, 50.6, 50.3, 50.0, 50.0, 46.3, 45.6, 41.8, 40.8, 40.2, 39.9, 39.8, 38.7, 37.2, 36.1, 34.2, 31.9, 30.9, 30.5, 29.7, 29.6, 28.9, 27.9, 27.7, 27.5, 26.5, 26.1, 24.2, 22.9, 22.7, 21.3, 21.1, 21.1, 20.5, 17.6, 16.3

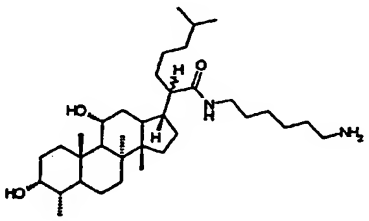
39/139	A	16(17)-en-16-desacetoxy-tetrahydro fusidic acid- *N*-succinimide ester	spermine	

^{13}C NMR (CD_3OD), δ/ppm: *(1:1 mixture of C-20 epimers)*

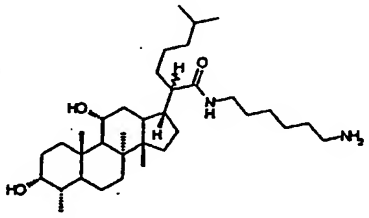
176.5, 176.3, 145.7, 145.6, 125.7, 125.3, 72.5, 69.3, 69.2, 55.1, 55.0, 51.9, 51.8, 50.4, 50.4, 47.8,

47.7, 44.8, 44.4, 41.4, 41.4, 40.6, 40.5, 40.0, 39.8, 39.7, 38.3, 38.0, 37.9, 37.4, 34.0, 34.0, 33.4, 32.4, 31.3, 31.2, 30.2, 30.2, 29.2, 28.1, 26.9, 26.8, 25.3, 25.3, 23.5, 23.4, 23.1, 23.0, 23.0, 22.4, 18.1, 18.0, 16.6

MS (direct inlet) m/z = 645.58 $(M+H)^+$, 569.53, 321.54, 305.55, 203.21

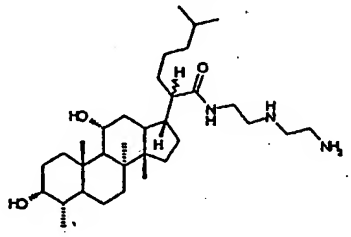
40/140	A	16-Desacetoxy tetrahydrofusidic acid-*N*-succinimide ester	1,6-hexanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 178.0, 72.6, 69.5, 52.3, 51.8, 51.7, 43.9, 42.0, 41.7, 40.2, 40.1, 38.2, 38.0, 37.5, 37.1, 33.2, 33.0, 32.1, 31.4, 31.1, 30.6, 29.2, 27.8, 27.4, 26.9, 26.6, 23.8, 23.3, 23.1, 23.0, 22.7, 16.6, 16.4

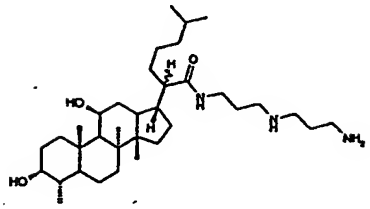
41/141	A	16-Desacetoxy tetrahydrofusidic acid-*N*-succinimide ester	1,6-hexanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 178.5, 72.5, 69.4, 53.9, 51.8, 51.7, 43.8, 42.4, 42.2, 41.5, 40.2, 40.1, 38.3, 37.9, 37.1, 36.7, 33.1, 33.0, 32.5, 31.6, 31.1, 31.1, 30.3, 29.2, 28.5, 28.0, 27.6, 26.5, 23.9, 23.2, 23.2, 22.9, 22.7, 16.6, 16.4

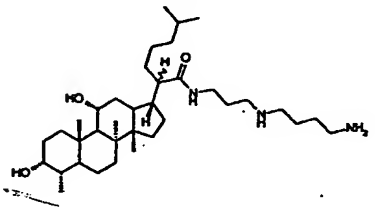
Comment: C-20 epimer of Compound 137.

42/142	A	16-Desacetoxy tetrahydrofusidic acid-*N*-succinimide ester	diethylenetriamine	

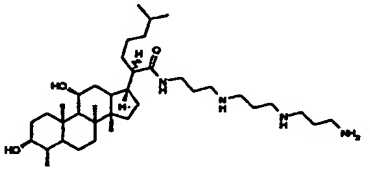
^{13}C NMR (CD_3OD), δ/ppm: 178.9, 72.5, 69.3, 54.5, 51.9, 51.7, 43.7, 42.6, 41.6, 41.5, 40.1, 38.2, 38.0, 37.1, 36.9, 33.1, 32.9, 31.7, 31.2, 31.1, 29.1, 28.9, 26.5, 23.8, 23.3, 23.2, 22.9, 22.6, 16.6, 16.5

43/143	A	16-Desacetoxy tetrahydrofusidic acid-*N*-succinimide ester	3,3'-diamino-dipropylamine	

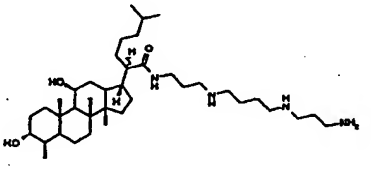
^{13}C NMR (CD_3OD), δ/ppm: 178.7, 72.5, 69.3, 54.1, 51.8, 51.7, 48.1, 43.8, 42.4, 41.5, 40.6, 40.2, 38.3, 38.2, 38.0, 37.1, 36.8, 33.1, 32.7, 32.6, 31.7, 31.2, 31.1, 30.1, 29.2, 28.6, 26.6, 23.8, 23.2, 22.9, 22.7, 16.6, 16.4

44/144	A	16-Desacetoxy tetrahydrofusidic acid-*N*-succinimide ester	spermidine	

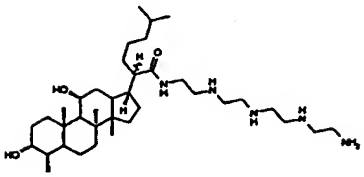
^{13}C NMR (CD_3OD), δ/ppm: 178.7, 72.5, 69.3, 54.0, 51.8, 51.7, 50.3, 47.9, 43.8, 42.4, 42.0, 41.5, 40.2, 38.3, 38.1, 38.0, 37.1, 36.8, 33.1, 32.5, 31.6, 31.2, 31.1, 30.5, 30.0, 29.2, 28.6, 27.8, 26.6, 23.8, 23.2, 22.9, 22.7, 16.6, 16.4

45/145	A	16-Desacetoxy tetrahydrofusidic acid-*N*-succinimide ester	N,N'-bis(3-aminopropyl)-1,3-propanediamine	

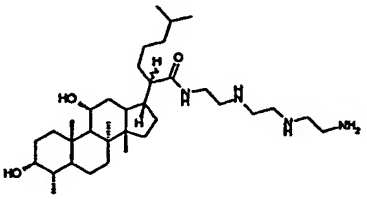
^{13}C NMR (CD_3OD), δ/ppm: 178.7, 72.5, 69.3, 54.0, 51.8, 51.7, 48.1, 43.9, 42.4, 41.5, 40.5, 40.2, 38.3, 38.2, 38.0, 37.1, 36.8, 33.1, 32.5, 31.8, 31.7, 31.2, 31.1, 30.1, 29.7, 29.2, 28.6, 26.6, 23.8, 23.2, 22.9, 22.7, 16.6, 16.4

46/146	A	16-Desacetoxy tetrahydrofusidic acid-*N*-succinimide ester	spermine	

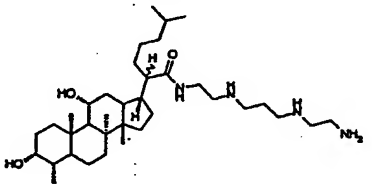
^{13}C NMR (CD_3OD), δ/ppm: 178.9, 72.5, 69.3, 53.9, 51.8, 51.7, 50.1, 48.0, 47.7, 43.9, 42.4, 41.5, 40.3, 40.2, 38.3, 38.0, 37.1, 36.8, 33.1, 32.5, 31.7, 31.2, 31.1, 30.4, 29.6, 29.2, 28.6, 27.6, 26.6, 23.8, 23.2, 23.0, 22.7, 16.6, 16.4

47/147	A	16-Desacetoxy tetrahydrofusidic acid-*N*-succinimide ester	tetraethylene-pentamine	

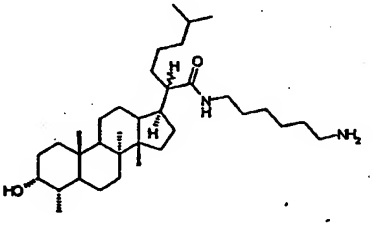
^{13}C NMR (CD_3OD), δ/ppm: 178.9, 72.5, 69.3, 54.4, 51.8, 51.1, 43.6, 42.6, 41.5, 41.3, 40.1, 38.2, 38.0, 37.1, 33.1, 32.9, 31.7, 31.2, 31.1, 29.1, 28.9, 26.5, 23.8, 23.4, 23.2, 22.9, 22.6, 16.6, 16.5

48/148	A	16-Desacetoxy tetrahydrofusidic acid-*N*-succinimide ester	tetraethylene-pentamine	

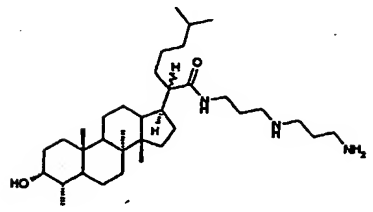
^{13}C NMR (CD_3OD), δ/ppm: 178.9, 72.5, 69.3, 54.5, 51.9, 51.7, 51.3, 43.6, 42.6, 41.6, 41.4, 40.1, 38.3, 38.0, 37.1, 36.9, 33.0, 32.9, 31.7, 31.2, 31.1, 29.1, 28.9, 26.5, 23.9, 23.3, 23.2, 22.9, 22.7, 16.6, 16.4

49/149	A		N,N'-bis(2-aminoethyl)-1,3-propanediamine	

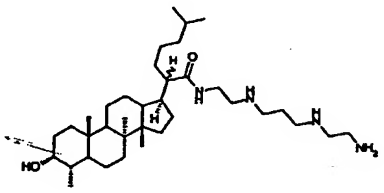
^{13}C NMR (CD_3OD), δ/ppm: 178.9, 72.5, 69.3, 54.4, 52.1, 51.8, 51.7, 48.7, 48.6, 43.7, 42.6, 41.6, 41.4, 40.1, 40.0, 38.3, 38.0, 37.1, 36.9, 33.1, 32.8, 31.7, 31.2, 31.1, 30.2, 29.1, 28.8, 26.5, 23.9, 23.3, 23.2, 22.9, 22.7, 16.6, 16.4

50/150	A	11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusidic acid *N*-succinimide ester	1,6-hexanediamine	

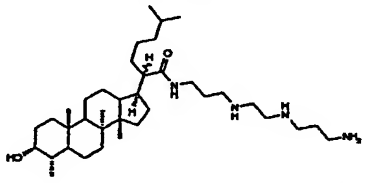
^{13}C NMR (CD_3OD), δ/ppm: 178.4, 72.5, 54.7, 52.0, 47.5, 46.4, 44.5, 42.4, 40.6, 40.2, 40.1, 39.0, 37.5, 36.4, 34.6, 33.4, 33.0, 31.7, 31.1, 30.3, 30.0, 29.2, 29.0, 28.1, 27.8, 27.3, 26.5, 24.7,23.2, 22.9, 21.5, 21.4, 20.7, 17.2, 16.6

51/151	A	11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusidic acid *N*-succinimide ester	3,3'-diamino-dipropylamine	

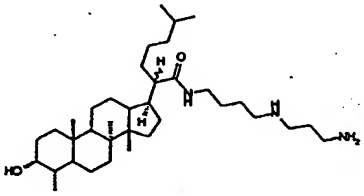
^{13}C NMR (CD_3OD), δ/ppm: 178.6, 72.5, 54.5, 52.0, 47.5, 46.4, 44.5, 40.7, 40.1, 39.0, 38.2, 37.5, 36.3, 34.6, 33.0, 32.8, 31.7, 31.2, 30.1, 30.0, 29.1, 28.8, 27.3, 26.6, 24.7, 23.2, 22.9, 21.5, 21.4, 20.7, 17.2, 16.6

52/152	A	11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusidic acid *N*-succinimide ester	N,N'-bis(2-aminoethyl)-1,3-propanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 178.8, 72.5, 54.6, 52.3, 52.0, 47.5, 46.4, 44.5, 41.6, 40.7, 40.1, 39.8, 39.0, 37.5, 36.4, 34.6, 32.9, 31.7, 31.2, 30.5, 30.0, 29.1, 28.8, 27.3, 26.5, 24.7, 23.2, 22.9, 21.5, 21.4, 20.7, 17.2, 16.6

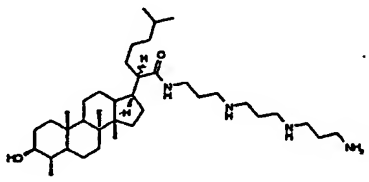
53/153	A	11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusidic acid *N*-succinimide ester	N,N'-bis(3-aminopropyl)-ethylenediamine	

^{13}C NMR (CD_3OD), δ/ppm: 178.6, 72.5, 54.5, 52.0, 49.7, 48.3, 47.5, 46.4, 44.5, 40.7, 40.6, 40.1, 39.0, 38.2, 37.5, 36.4, 34.6, 32.8, 31.7, 31.2, 30.3, 30.0, 29.1, 28.8, 27.3, 26.6, 24.7, 23.2, 22.9, 21.5, 21.4, 20.7, 17.2, 16.6

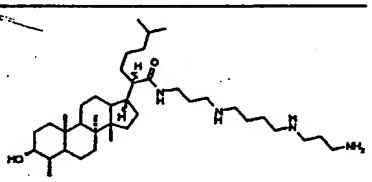
54/154	A	11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusidic acid *N*-succinimide ester	spermidine	

^{13}C NMR (CD_3OD), δ/ppm: 178.7, 72.5, 54.5, 52.0, 50.5, 48.1, 47.5, 46.4, 44.5, 42.1, 40.6, 40.1, 39.0, 38.2, 37.5, 36.3, 34.6, 32.8, 31.7, 31.2, 30.8, 30.0, 29.2, 28.8, 27.9, 27.3, 26.6, 24.7, 23.2, 22.9,

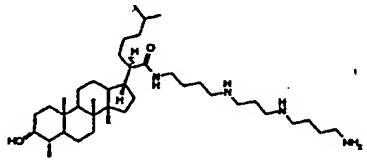
21.5, 21.4, 20.7, 17.2, 16.6

55/155	A	11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusidic acid *N*-succinimide ester	N,N'-bis(3-aminopropyl)-1,3-propanediamine	

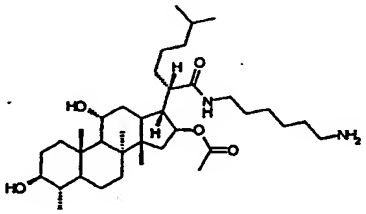
^{13}C NMR (CD_3OD), δ/ppm: 178.6, 72.5, 54.5, 52.0, 48.9, 48.3, 47.4, 46.3, 44.5, 40.6, 40.5, 40.1, 39.0, 38.2, 37.5, 36.3, 34.6, 32.8, 32.4, 31.7, 31.2, 30.1, 30.0, 29.9, 29.1, 28.8, 27.3, 26.5, 24.7, 23.2, 22.9, 21.5, 21.4, 20.7, 17.2,
16.6

56/156	A	11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusidic acid *N*-succinimide ester	spermine	

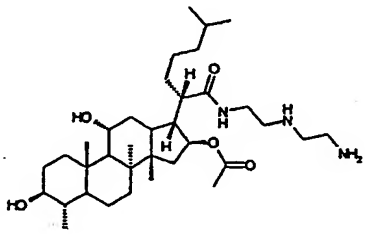
^{13}C NMR (CD_3OD), δ/ppm: 178.7, 72.5, 54.5, 52.0, 50.6, 50.4, 48.1, 47.4, 46.4, 44.5, 40.6, 40.6, 40.1, 39.0, 38.2, 37.5, 36.3, 34.6, 32.8, 32.4, 31.7, 31.2, 30.0, 29.1, 28.8, 28.3, 28.1, 27.3, 26.6, 24.7, 23.2, 22.9, 21.5, 21.4, 20.7, 17.2, 16.6

57/157	A	11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusidic acid *N*-succinimide ester	N,N'-bis(4-aminobutyl)-1,3-propanediamine	

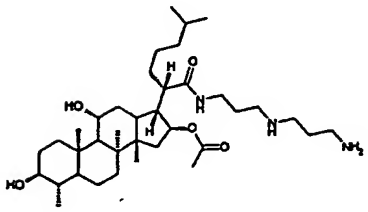
^{13}C NMR (CD_3OD), δ/ppm: 178.5, 72.5, 54.6, 52.0, 50.4, 50.3, 47.5, 46.4, 44.5, 42.2, 40.6, 40.1, 39.0, 37.5, 36.3, 34.6, 32.9, 31.7, 31.2, 31.0, 30.0, 30.0, 29.1, 28.9, 28.2, 28.0, 27.8, 27.3, 26.5, 24.7, 23.2, 22.9, 21.5, 21.4, 20.7, 17.2, 16.6

58/158	A	3β-OH-tetrahydrofusidic acid-*N*-succinimide ester	1,6-hexanediamine	

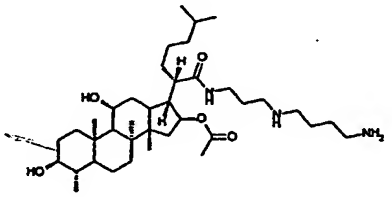
^{13}C NMR (CD_3OD), δ/ppm: 177.3, 172.6, 80.0, 77.3, 68.8, 51.3, 51.0, 50.3, 50.1, 44.2, 42.3, 41.5, 41.3, 41.2, 41.1, 40.3, 40.1, 37.9, 37.7, 36.5, 35.2, 33.7, 33.3, 32.6, 31.7, 30.3, 29.2, 28.0, 27.7, 26.4, 24.5, 23.6, 23.1, 23.0, 22.7, 21.4, 17.1, 15.9

59/159	A	3β-OH-tetrahydrofusidic acid-*N*-succinimide ester	diethylenetriamine	

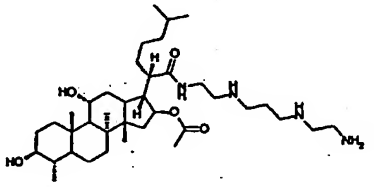
^{13}C NMR (CD_3OD), δ/ppm: 178.1, 173.0, 80.8, 77.8, 69.1, 52.2, 51.4, 50.8, 50.6, 44.7, 42.1, 42.0, 41.7, 41.6, 41.5, 40.6, 40.5, 38.2, 37.1, 35.7, 34.1, 33.1, 32.3, 29.5, 26.7, 24.9, 24.1, 23.5, 23.3, 23.1, 21.8, 17.6, 16.4

60/160	A	3β-OH-tetrahydrofusidic acid-*N*-succinimide ester	3,3'-diamino-dipropylamine	

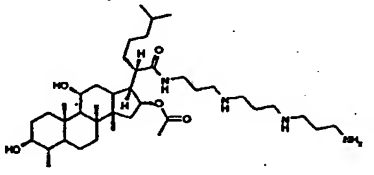
^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 80.2, 77.3, 68.7, 51.6, 50.9, 50.3, 50.2, 48.4, 44.3, 41.6, 41.3, 41.2, 41.1, 40.6, 40.1, 38.3, 37.7, 36.6, 35.3, 33.7, 33.2, 32.6, 31.8, 30.2, 29.1, 26.4, 24.5, 23.6, 23.2, 23.0, 22.7, 21.4, 17.1, 15.9

61/161	B	3β-OH-tetrahydrofusidic acid-*N*-succinimide ester	spermidine	

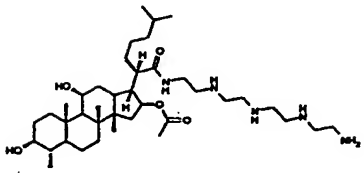
^{13}C NMR (CD_3OD), δ/ppm:

62/162	B	3β-OH-tetrahydrofusidic acid-*N*-succinimide ester	N,N'-bis(2-aminoethyl)-1,3-propanediamine	

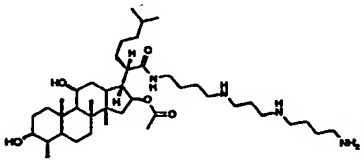
^{13}C NMR (CD_3OD), δ/ppm: 178.1, 173.0, 80.8, 77.7, 69.2, 52.4, 52.2, 51.4, 50.8, 50.6, 49.0, 44.7, 42.0, 41.8, 41.7, 41.6, 41.5, 40.5, 40.4, 38.2, 37.0, 35.7, 34.1, 33.1, 32.3, 30.7, 29.5, 26.7, 24.9, 24.1, 23.5, 23.3, 23.1, 21.8, 17.6, 16.3

63/163	A	3β-OH-tetrahydrofusidic acid-*N*-succinimide ester	N,N'-bis(3-aminopropyl)-1,3-propanediamine	

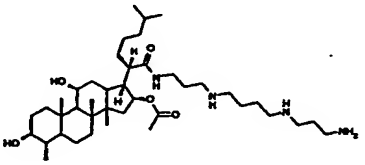
^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 80.2, 77.3, 68.7, 51.5, 50.9, 50.3, 50.2, 44.3, 41.5, 41.3, 41.2, 41.1, 40.5, 40.1, 38.2, 37.7, 36.6, 35.3, 33.7, 32.6, 32.0, 31.8, 30.1, 29.8, 29.1, 26.4, 24.5, 23.6, 23.2, 23.0, 22.7, 21.4, 17.1, 16.0

64/164	A	3β-OH-tetrahydrofusidic acid-*N*-succinimide ester	tetraethylene-pentamine	

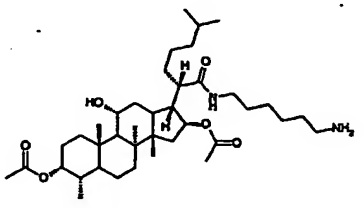
^{13}C NMR (CD_3OD), δ/ppm: 177.7, 172.5, 80.4, 77.3, 68.7, 51.8, 51.0, 50.4, 50.1, 44.3, 41.7, 41.3, 41.2, 40.1, 37.8, 36.7, 35.3, 33.7, 32.7, 31.9, 29.1, 26.3, 24.5, 23.7, 23.1, 22.9, 22.7, 21.4, 17.2, 16.0

65/165	A	3β-OH-tetrahydrofusidic acid-*N*-succinimide ester	N,N'-bis(4-aminobutyl)-1,3-propanediamine	

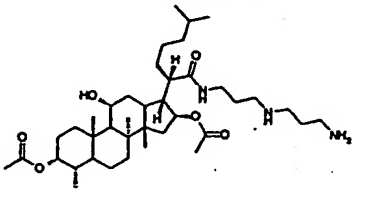
^{13}C NMR (CD_3OD), δ/ppm:

66/166	A	3β-OH-tetrahydrofusidic acid-*N*-succinimide ester	spermine	

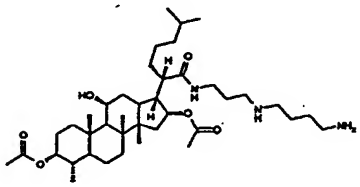
^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.5, 80.2, 77.3, 68.7, 51.5, 50.9, 50.4, 50.3, 50.2, 47.9, 44.2, 41.5, 41.3, 41.2, 41.1, 40.4, 40.1, 38.2, 37.7, 36.6, 35.2, 33.6, 32.6, 31.7, 30.0, 29.1, 28.1, 27.9, 26.4, 24.5, 23.6, 23.2, 23.0, 22.7, 21.4, 17.1, 16.0

67/167	A	3-acetoxy-tetrahydrofusidic acid	1,6-hexanediamine	

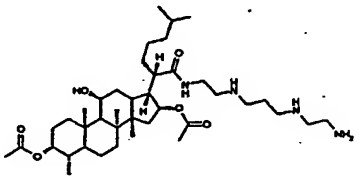
^{13}C NMR (CD_3OD), δ/ppm: 177.3, 172.9, 172.6, 80.1, 76.2, 68.6, 51.4, 51.1, 50.3, 50.2, 42.3, 41.5, 41.3, 41.1, 40.3, 40.1, 38.9, 38.0, 36.6, 36.6, 33.5, 33.2, 31.7, 30.3, 29.2, 28.3, 28.0, 27.7, 26.4, 23.7, 23.4, 23.1, 23.0, 22.3, 21.4, 21.2, 17.2, 16.1

68/168	A	3-acetoxy-tetrahydrofusidic acid	3,3'-diamino-dipropylamine	

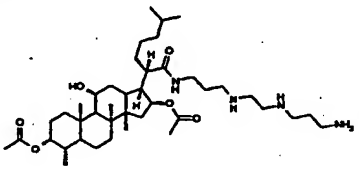
^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.9, 172.6, 80.3, 76.2, 68.6, 51.6, 51.0, 50.4, 50.2, 48.4, 41.5, 41.3, 41.1, 40.6, 40.1, 38.9, 38.3, 38.0, 36.7, 36.6, 33.5, 33.1, 31.8, 31.7, 30.2, 29.2, 28.3, 26.4, 23.7, 23.4, 23.2, 23.0, 22.3, 21.4, 21.2, 17.2, 16.1

69/169	A	3-acetoxy-tetrahydrofusidic acid	spermidine	

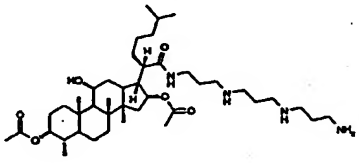
^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.9, 172.6, 80.3, 76.2, 68.6, 51.6, 51.0, 50.5, 50.4, 50.2, 48.1, 42.3, 41.5, 41.3, 41.1, 40.1, 38.9, 38.3, 38.0, 36.7, 36.6, 33.5, 31.8, 31.7, 31.2, 30.1, 29.2, 28.3, 27.9, 26.4, 23.7, 23.4, 23.2, 23.0, 22.3, 21.4, 21.2, 17.2, 16.1

70/170	A	3-acetoxy-tetrahydrofusidic acid	N,N'-bis(2-aminoethyl)-1,3-propanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.7, 172.9, 172.6, 80.4, 76.2, 68.6, 52.3, 51.8, 51.1, 50.4, 50.2, 48.6, 41.6, 41.6, 41.3, 41.1, 40.1, 38.9, 38.0, 36.7, 36.6, 33.6, 31.9, 31.8, 30.4, 29.1, 28.3, 26.3, 23.8, 23.4, 23.1, 22.9, 22.2, 21.4, 21.2, 17.3, 16.1

71/171	A	3-acetoxy-tetrahydrofusidic acid	N,N'-bis(3-aminopropyl)-ethylenediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.9, 172.6, 80.3, 76.2, 68.6, 51.6, 51.1, 50.4, 50.2, 49.9, 49.8, 48.4, 41.6, 41.3, 41.1, 40.6, 40.1, 38.9, 38.3, 38.0, 36.7, 36.6, 33.5, 33.0, 31.8, 31.8, 30.3, 29.2, 28.3, 26.4, 23.7, 23.4, 23.2, 23.0, 22.3, 21.4, 21.2, 17.3, 16.1

72/172	A	3-acetoxy-tetrahydrofusidic acid	N,N'-bis(3-aminopropyl)-1,3-propanediamine	

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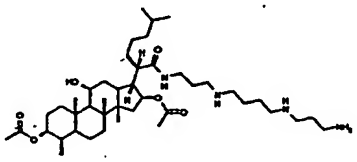
41.6, 41.3, 41.1, 40.6, 40.1, 38.9, 38.3, 38.0, 36.7, 36.6, 33.5, 32.9, 31.9, 31.7, 30.2, 29.2, 28.3, 26.4, 23.7, 23.4, 23.2, 23.0, 22.3, 21.4, 21.2, 17.3, 16.1

73/173	A	3-acetoxy-tetrahydrofusidic acid	spermine	

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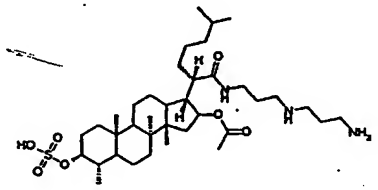
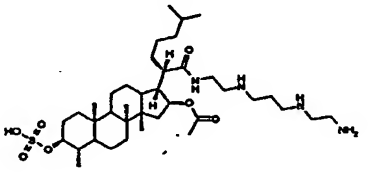
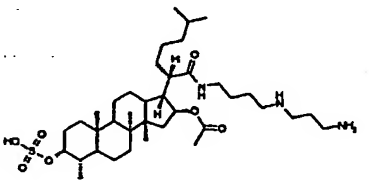
74/174	A	3-OSO_3H-11-desoxy-tetrahydrofusidic acid *N*-succinimide ester	3,3'-diamino-dipropylamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 81.7, 81.2, 52.3, 51.0, 50.7, 46.6, 46.1, 41.0, 40.5, 40.0, 39.9, 39.5, 38.1, 37.0, 36.2, 33.8, 32.6, 30.5, 29.5, 29.1, 28.4, 28.0, 26.9, 26.4, 24.7, 23.1, 22.9, 21.6, 21.4, 21.2, 17.8, 16.4

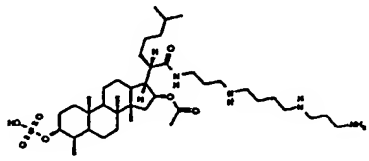
75/175	A	3-OSO_3H-11-desoxy-tetrahydrofusidic acid *N*-succinimide ester	N,N'-bis(2-aminoethyl)-1,3-propanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.7, 172.6, 81.7, 81.2, 52.5, 51.0, 50.7, 46.8, 46.1, 41.0, 40.5, 40.0, 39.7, 39.6, 37.1, 36.1, 33.9, 32.6, 30.5, 29.7, 29.1, 28.4, 27.0, 26.3, 24.7, 23.1, 22.9, 21.7, 21.4, 21.2, 21.1, 17.8, 16.4

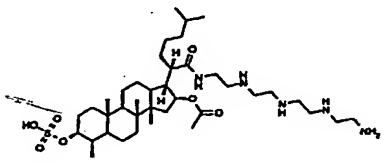
76/176	A	3-OSO_3H-11-desoxy-tetrahydrofusidic acid *N*-succinimide ester	spermidine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 81.7, 81.5, 52.6, 51.0, 50.8, 50.4, 46.7, 46.1, 40.9, 40.8, 40.5, 40.0, 39.5, 38.2, 37.1, 36.1, 33.8, 32.7, 30.5, 29.3, 29.1, 28.4, 27.3, 27.2, 27.0, 26.4, 24.7, 23.1,

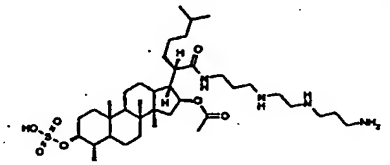
22.9, 21.6, 21.4, 21.2, 21.1, 17.8, 16.4

77/177	A	3-OSO_3H-11-desoxy-tetrahydrofusidic acid *N*-succinimide ester	spermine	

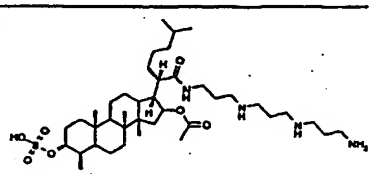
^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 81.7, 81.5, 52.6, 51.0, 50.8, 50.6, 47.8, 46.7, 46.0, 40.9, 40.5, 40.0, 40.0, 39.6, 38.2, 37.1, 36.1, 33.9, 32.8, 30.5, 29.1, 28.7, 28.5, 27.6, 27.1, 27.0, 26.4, 24.7, 23.1, 22.9, 21.6, 21.3, 21.2, 21.1, 17.8, 16.4

78/178	A	3-OSO_3H-11-desoxy-tetrahydrofusidic acid *N*-succinimide ester	tetraethylene-pentamine	

NMR (CD_3OD), δ/ppm: 177.6, 172.6, 81.7, 81.1, 53.6, 52.3, 50.9, 50.7, 46.6, 46.1, 40.9, 40.5, 40.0, 39.6, 37.1, 36.1, 33.9, 32.6, 30.4, 29.1, 28.4, 27.0, 26.3, 24.7, 23.1, 23.0, 22.9, 21.7, 21.4, 21.2, 21.1, 17.8, 16.4

79/179	A	3-OSO_3H-11-desoxy-tetrahydrofusidic acid *N*-succinimide ester	N,N'-bis(3-aminopropyl)-ethylenediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 81.7, 81.1, 52.3, 50.9, 50.7, 48.0, 46.6, 46.0, 40.9, 40.5, 40.0, 39.6, 38.1, 37.1, 36.1, 33.9, 32.5, 30.4, 29.6, 29.1, 28.4, 28.3, 26.9, 26.4, 24.7, 23.1, 22.9, 21.6, 21.3, 21.2, 21.1, 17.8, 16.4

80/180	A	3-OSO_3H-11-desoxy-tetrahydrofusidic acid *N*-succinimide ester	N,N'-bis(3-aminopropyl)-1,3-propanediamine	

^{13}C NMR (CD_3OD), δ/ppm: 177.5, 172.6, 81.8, 81.3, 52.5, 51.0, 50.7, 48.3, 47.9, 46.6, 46.0, 40.9, 40.5, 40.0, 39.9, 39.6, 38.2, 37.1, 36.1, 33.9, 32.7, 32.3, 30.4, 29.5, 29.1, 28.7, 28.7, 28.4, 27.0, 26.4, 23.1, 22.9, 21.6, 21.3, 21.2, 21.1, 17.8, 16.4

Example 81: Cream

Compound 125	1 g
Petrolatum	7.5 g
Liquid paraffin	7.5 g
Spermaceti	2.5 g
Sorbitane monopalmitate	2.5 g
Polyoxyethylene sorbitane monopalmitate	2.5 g
Water	26.5 g
	50 g

Heat petrolatum, paraffin, spermaceti, sorbitane monopalmitate and polyoxyethylene sorbitane monopalmitate to 70°C and slowly add water under continuous stirring. Continue stirring until the cream has cooled. Triturate compound 125 into the cream base and homogenise using a roller mill. Fill the cream into aluminium collapsible tubes.

Example 82: Ointment

Compound 146	1 g
Liquid paraffin	6.9 g
Cetanol	0.2 g
Lanolin anhydrous	2.3 g
Petrolatum	39.6 g
	50 g

Melt paraffin, cetanol, lanolin and petrolatum at 70°C. After cooling to below 40 °C compound 149. Fill the ointment into lacquered collapsible aluminium tubes.

Example 83: Capsules

Compound 177	25 g
Microcrystalline cellulose	14.5 g
Magnesium stearate	0.5 g
	40 g

Pass the ingredients through a 60 mesh sieve and mix for 10 min. Fill the mixture into hard gelatine capsules using a capsule fill weight of 400 mg.

Example 84: Tablets

Compound 125	25 g
Avicel™	12 g
STA-Rx 1500	12 g
Magnesium stearate	1 g
	50 g

Compound 125 Avicel™ and STA-Rx are mixed together, sieved through a 0.7 mm sieve and thereafter mixed with magnesium stearate: The mixture is pressed into tablets each of 500 mg.

Example 85: Suspension

Compound 180	1 g
Citric acid	0.09 g
Sodium monohydrogenphosphate	0.14 g
Sucrose	5 g
Tween™ 80	0.01 g
Potassium sorbate	0.04 g
Carboxymethylcellulose-Na	0.1 g
Water	qs. to 100 ml suspension.

The crystals are micronized and suspended in a solution of citric acid, sodium monohydrogen phosphate, sucrose, potassium sorbate and Tween™ 80 in 10 ml water, if necessary with slight warming. Carboxymethylcellulose-Na is dissolved in 4 ml boiling water. After cooling, it is added to the other ingredients. The suspension is homogenised in a blender and finally water is added to a total volume of 100 ml.

Example 86: Ointment

A: 11-Compound 145	1 g
B: One of the compounds: hydrocortisone, triamcinolone or fluocinolone	0.5 g
Liquid paraffin	6.9 g
Cetanol	0.2 g
Lanolin anhydrous	2.3 g
Petrolatum	39.1 g
	50 g

Melt paraffin, cetanol, lanolin and petrolatum at 70°C. After cooling to below 40 °C, triturate A and B. Fill the ointment into lacquered collapsible aluminium tubes.

Example 87: Ointment

A: Compound 172	1.5 g
B: Tetracycline	1.5 g
Liquid paraffin	13.8 g
Cetanol	0.4 g
Lanolin anhydrous	4.6 g
Petrolatum	78.2 g
	100 g

Melt paraffin, cetanol, lanolin and petrolatum at 70°C. After cooling to below 40 °C, triturate A and B. Fill the ointment into lacquered collapsible aluminium tubes.

Example 88: Eye gel

Compound 177	10 g
Benzalkonium chloride	0.1 g
Carbomer	5 g
Mannitol	50 g
Sodium edetate	0.5 g
Sodium hydroxide	q.s.
Sterile water	up to 100 g

Dissolve disodium edetate and mannitol in water for injection in a stainless steel vessel equipped with a stirring tool and a built-in homogenizer. Add Carbomer 934P, evacuate the vessel and

autoclave the dispersion under slow stirring and homogenizing at high speed. Cool down to 70 °C, stop agitator and homogenizer. Add compound 177, sodium salt micronized, sterile - evacuate the vessel and let the 17S,20S-Methanofusidic acid, sodium salt sink during slow agitation. Homogenize at high speed for 10 minutes at 70 °C. Cool down to below 30 °C during stirring and homogenizing at low speed. Add a sterile solution of benzalkonium chloride in water for injection under slow stirring. Neutralise the carbomer 934 P by adding a sterile solution of sodium hydroxide 1.050 kg in water for injection. Stir and homogenize at low speed for 5 minutes. Adjust - if necessary - the pH to 5.4 - 5.8. Transfer the eye gel to storage tanks using nitrogen pressure and the low speed homogenizing transfer system. Store at room temperature until filling. The eye gel is filled aseptically in sterile tubes using a fill weight of 3.5 g.

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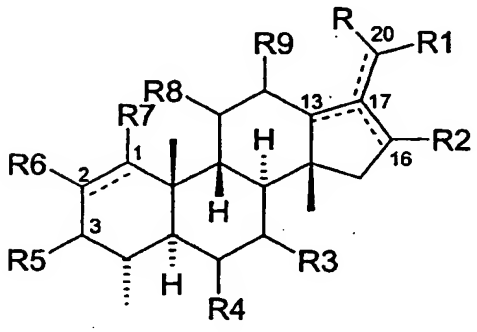
CLAIMS

1. A compound of the general formula I



I

wherein

R_1 is hydrogen, halogen, CH_3, CH_2-OH, COOH, CH_2-OSO_3, CH_2–NH-$(CH_2)_a$-R_{10}, or C(=O)–NH-$(CH_2)_a$-R_{10} wherein R_{10} is –NH_2, -NH-$(CH_2)_b$-NH_2, –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH_2, –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH_2, –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH-$(CH_2)_e$-NH_2, –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH-$(CH_2)_e$NH-$(CH_2)_f$-NH_2, a saturated or unsaturated heterocyclic ring comprising 1 or 2 heteroatoms, or –NH-$(CH_2)_b$-R_{11}, wherein R_{11} is a saturated or unsaturated heterocyclic ring comprising 1 or 2 heteroatoms, and a, b, c, d, e and f are the same or different and individually represent integers of from 1 to 5;

R_2 is hydrogen, halogen, -OH or –OR_{12}, wherein R_{12} is SO_3, C_{1-6} alkyl or C_{1-6} acyl, –NH-$(CH_2)_a$-R_{10};

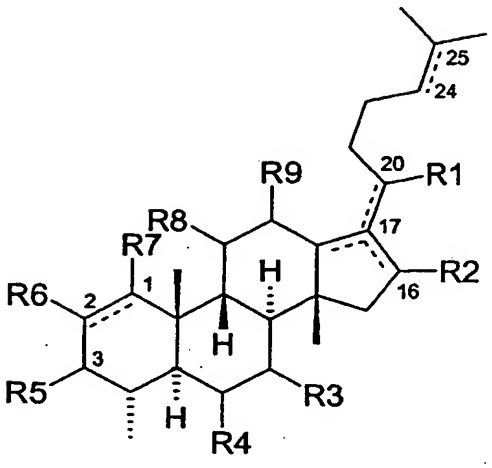
R is hydrogen, halogen, a lipophilic group, –NH_2-$(CH_2)_a$-R_{10} or CH_2–NH-$(CH_2)_a$-R_{10};

R_4, R_5, R_6, R_7 and R_9 are the same or different and individually represent hydrogen, halogen, -OH, -OSO_3 or –NH-$(CH_2)_a$-R_{10};

R_3 and R_8 are the same or different and individually represent hydrogen, halogen, -OH or OSO_3; and the dotted lines between carbon atoms 1 and 2, 13 and 17, 16 and 17, and 17 and 20 indicate the presence of a single or double bond;

provided that at least one and not more than two of R, R_1, R_2, R_4, R_5, R_6, R_7 or R_9 is –NH-$(CH_2)_a$-R_{10}, CH_2–NH-$(CH_2)_a$-R_{10} or C(=O)–NH-$(CH_2)_a$-R_{10}, and the others are hydrogen, -OH or –OSO_3, or (for R_2) –OR_{12}; and further provided that at least one and not more than four of R_2-R_9 are –OH or –OSO_3; and pharmaceutically acceptable salts and esters thereof.

2. A compound according to claim 1 which has the general formula Ia



Ia

wherein

R_1 is CH_3, CH_2–NH-$(CH_2)_a$-R_{10} or C(=O)–NH-$(CH_2)_a$-R_{10}, wherein R_{10} and a are as indicated above; R_2 and R_5 are hydrogen, -OH or $-OSO_3$, or (for R_2) $-OR_{12}$, wherein R_{12} is as indicated above; R_3, R_4, R_6, R_8 and R_9 are hydrogen, -OH or $-OSO_3$; and the dotted line between carbon atoms 1 and 2, 13 and 17, 16 and 17, 17 and 20, and 24 and 25 indicates the presence of a single or double bond; provided that at least one and not more than four of R_2, R_3, R_4, R_5, R_6, R_8 and R_9 are –OH or OSO_3.

3. A compound according to claim 1 or 2, wherein a is 2 or 3.

4. A compound according to any of claims 1-3, wherein R_{10} is –NH-$(CH_2)_b$-NH_2, wherein b has the meaning indicated in claim 1.

5. A compound according to any of claims 1-4, wherein b is 3 or 4.

6. A compound according to any of claims 1-3, wherein R_{10} is –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH_2, wherein b and c are as indicated in claim 1.

7. A compound according to any of claims 1-6, wherein c is 2 or 3.

8. A compound according to any of claims 1-3, wherein R_{10} is –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH_2, wherein b, c and d are as indicated in claim 1.

9. A compound according to any of claims 1-8, wherein d is 2, 3 or 4.

10. A compound according to any of claims 1-3, wherein R_{10} is –NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH-$(CH_2)_e$-NH_2, wherein b, c, d and e are as indicated in claim 1.

11. A compound according to any of claims 1-10, wherein e is 2, 3 or 4.

12. A compound according to claim 1 or 2, wherein R_1 is –NH-$(CH_2)_3$-NH-$(CH_2)_4$-NH-$(CH_2)_3$-NH_2, CH_2–NH-$(CH_2)_3$-NH-$(CH_2)_4$-NH-$(CH_2)_3$-NH_2 or C(=O)–NH-$(CH_2)_3$-NH-$(CH_2)_4$-NH-$(CH_2)_3$-NH_2.

13. A compound according to any of claims 1-12, wherein R_2 is –OR_{12}.

14. A compound according to claim 13, wherein R_{12} is C_{1-6} alkyl or C_{1-6} acyl.

15. A compound according to claim 13, wherein R_{12} is –NH-$(CH_2)_a$-R_{10}, CH_2–NH-$(CH_2)_a$-R_{10} or C(=O)-NH-$(CH_2)_a$$R_{10}$.

16. A compound according to any of claims 1-15, wherein R_3, R_5 and/or R_8 are an –OH group.

17. A compound according to claim 1, wherein R is branched or straight C_{1-10} alkyl, aryl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aralkyl with 1-10 carbon atoms in the alkyl moiety, C_{1-10} alkylaryl, C_{1-10} alkyl-C_{3-8} cycloalkyl, C_{1-10} alkyl-C_{3-8} cycloalkenyl, C_{1-10} alkoxy or heteroaryl.

18. A compound according to claim 17, wherein R is as shown in formula Ia.

19. A compound according to any of claims 1-18 which is selected from the group consisting of

21-*N*-{3'-aminopropyl}-fusid-21-amide (Compound 101),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl}-fusid-21-amide (Compound 102),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-fusid-21-amide (Compound 103),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-fusid-21-amide (Compound 104),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-fusid-21-amide (Compound 105),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-fusid-21-amide (Compound 106),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-fusid-21-amide (Compound 107),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-fusid-21-amide (Compound 108),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-fusid-21-amide (Compound 109),

21-*N*-{6'-[(6'-aminohexyl)amino]hexyl}-fusid-21-amide (Compound 110),

21-*N*-{8'-[(8'-aminooctyl)amino]octyl}-fusid-21-amide (Compound 111),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-fusid-21-amide (Compound 112),

3-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-fusidic acid (Compound 113)

3-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-fusidic acid (Compound 114)

3-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]fusidic acid (Compound 115)

21-*N*-{2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl)amino}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 116),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 117),

21-*N*-{6'-aminohexyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 118),

21-*N*-{3'-aminopropyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 119),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 120),

21-*N*-{4'-[(3'-aminopropyl)amino]butyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 121),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 122),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 123),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 124),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 125),

21-*N*-{6'-[(6'-aminohexyl)amino]hexyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 126),

21-*N*-{8'-[(8'-aminooctyl)amino]octyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 127),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 128),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 129),

21-*N*-{6'-aminohexyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 130),

21-*N*-{3'-[3'-aminoproyl)amino]propyl }-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 131),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl }-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 132),

21-*N*-{2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 133),

21-*N*-{2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl)amino}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 134),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 135),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 136),

21-*N*-{4'-[(3'-aminopropyl)amino]butyl }-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 137),

21-*N*-{[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]}-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 138),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-16(17)-en-17,20,24,25-tetrahydrofusidan-21-carboxamide (Compound 139),

21-*N*-{6'-aminohexyl}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 140),

21-*N*-{6'-aminohexyl }-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 141), (C-20 epimer of Compound 140),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 142),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 143),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 144),

21-*N*-{[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 145),

21-*N*-{[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 146),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 147),

21-*N*-{2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl)amino}-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 148),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-16-desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 149),

21-*N*-{6'-aminohexyl}-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 150),

21-*N*-{3'-[3'-aminoproyl)amino]propyl }-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 151),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 152),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 153),

21-*N*-{4'-[(3'-aminopropyl)amino]butyl }-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 154),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 155),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 156),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-11-desoxy-16-desacetoxy-17S,20,24,25-tetrahydrofusid-21-amide (Compound 157),

21-*N*-{6'-aminohexyl}-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 158),

21-*N*-{2'-[(2'-aminoethyl)amino]ethyl}-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 159),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 160),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 161),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 162),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 163),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 164),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 165),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-3β- desacetoxy-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 166),

21-*N*-{6'-aminohexyl}-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 167),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 168),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 169),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 170),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 171),

21-*N*-[3'-({3'-[(3'-aminopropyl)amino]propyl}amino)propyl]-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 172),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-3-OAc-17R,20S,24,25-tetrahydrofusid-21-amide (Compound 173),

21-*N*-{3'-[3'-aminoproyl)amino]propyl}-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 174),

21-*N*-[2'-({3'-[(2'-aminoethyl)amino]propyl}amino)ethyl]-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 175),

21-*N*-{3'-[(4'-aminobutyl)amino]propyl}-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 176),

21-*N*-[3'-({4'-[(3'-aminopropyl)amino]butyl}amino)propyl]-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 177),

21-*N*-(2'-{[2'-({2'-[(2'-aminoethyl)amino]ethyl}amino)ethyl]amino}ethyl)-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 178),

21-*N*-[3'-({2'-[(3'-aminopropyl)amino]ethyl}amino)propyl]-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 179),

21-*N*-[4'-({3'-[(4'-aminobutyl)amino]propyl}amino)butyl]-3-OSO_3-11-desoxy-17,20,24,25-tetrahydrofusid-21-amide (Compound 180).

20. A pharmaceutical composition comprising a compound according to any of claims 1-19, optionally together with a pharmaceutically acceptable excipient or diluent, and optionally together with another therapeutically active agent.

21. A composition according to claim 20 which is in the form of a topical formulation.

22. A composition according to claim 21 which is a cream, ointment, salve or lotion.

23. A composition according to any of claims 20-23 wherein said other agent is selected from the group consisting of penicillins, cephalosporins, tetracyclins, rifamycins, erythromycins, lincomycin, clindamycin, fluoroquinolones, hydrocortisone and triamcinolone.

24. A compound according to any of claims 1-19 for use as a medicament.

25. A compound according to claim 24 for use as an antimicrobial agent.

26. A compound according to claim 25 for use as an antibacterial agent.

27. Use of a compound according to any of claims 1-19 for the preparation of a medicament for the prevention or treatment of infection.

28. The use according to claim 27 for the prevention or treatment of bacterial infection.

29. The use according to claim 27 or 28, wherein said compound is combined with one or more other therapeutically active agents.

30. The use according to any of claims 27-29, wherein the medicament is intended for topical administration.

31. A method of preventing or treating infection, the method comprising administering to a patient in need thereof an effective amount of a compound according to any of claims 1-19.

32. A method according to claim 30, wherein said infection is a bacterial infection.

33. A method according to claim 30 or 31, wherein said compound is administered topically.

34. A method according to any of claims 30-32, wherein said compound is administered together with one or more other therapeutically active agents.

35. A method according to claim 33 wherein said other therapeutically active agent is selected fro the group consisting of penicillins, cephalosporins, tetracyclins, rifamycins, erythromycins, lincomycin, clindamycin, fluoroquinolones, hydrocortisone and triamcinolone

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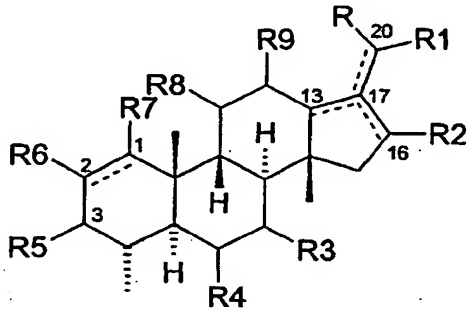
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL POLYAMINATED FUSIDIC ACID DERIVATIVES



(I)

(57) Abstract: Compounds of the general formula (I) wherein R_1 is hydrogen, halogen, CH¿3, CH2?-OH, COOH, CH_2-OSO_3,CH_2-NH-$(CH_2)_a$-R_{10}, or C(=O)-NH-$(CH_2)_a$-R_{10}wherein $R_{10}$is-NH_2,-NH-$(CH_2)_b$-NH_2, -NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH_2-NH-$(CH_2)_b$-NH$(CH_2)_c$-NH-$(CH_2)_d$-NH_2,-NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH-$(CH_2)_e$-NH_2,-NH-$(CH_2)_b$-NH-$(CH_2)_c$-NH-$(CH_2)_d$-NH-$(CH_2)_e$NH-$(CH_2)_f$-NH_2, a saturated or unsaturated heterocycling ring comprising 1 or 2 heteroatoms, or NH-$(CH_2)_b$-R¿11, ?wherein R_{11} is a saturated or unsaturated heterocyclic ring comprising 1 or 2 heteroatoms, and a, b, c, d, e and f are the same or different and individually represent integers of from 1 to 5; R_2 is hydrogen, halogen, -OH or OR_{12}, wherein R_{12} is SO_3, C_{1-6}alkyl or C_{1-6}acyl, -NH-$(CH_2)_a$-R_{10}; R is hydrogen, halogen, a lipophilic group, -NH_2-$(CH_2)_a$-R_{10} or CH_2-NH-$(CH_2)_a$-R_{10}; R_4, R_5, R_6, R_7 and R_9 are the same or different and individually represent hydrogen, halogen, -OH, -OSO_3 or NH-$(CH_2)_a$-R_{10}; R¿3 ?and R_8 are the same or different and individually represent hydrogen, halogen, -OH or OSO_3;and the dotted lines between carbon atoms 1 and 2, 13 and 17, 16 and 17, and 17 and 20 indicate the presence of a single or double bond; provided that at least one and not more than two of R, R_1, R_2, R_4, R_5, R_6, R_7 or R_9 is NH-$(CH_2)_a$-R_{10}, CH_2-NH-$(CH_2)_a$-R_{10} or C(=O)-NH-$(CH_2)_a$-R_{10}, and the others are hydrogen, -OH or OSO_3, or (for R_2)-OR_{12}; and further provided that at least one and not more than four of R_2-R_9 are-OH or OSO_3; and pharmaceutically acceptable salts and esters thereof are active against a broad spectrum of microorganisms, and may thereof be used in the treatment of microbial infections.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00183

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J41/00 A61K31/57 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEE W A ET AL: "THE SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL TESTING OF A NOVEL CLASS OF MUCOSAL PERMEATION ENHANCERS" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 22, no. 3, 1 November 1992 (1992-11-01), pages 223-237, XP000311550 ISSN: 0168-3659 compounds 3 and 4 ---	1-3,5,7, 9,11, 13-18
X	US 5 637 691 A (FRYE LEAH L ET AL) 10 June 1997 (1997-06-10) the whole document ---	1-34
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2002	28. 10. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Anna Sjölund

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 09137 A (MAGAININ PHARMA (US)) 24 February 2000 (2000-02-24) the whole document ---	1-34
A	US 4 162 259 A (WELF VON DAEHNE ET AL) 24 July 1979 (1979-07-24) the whole document -----	1-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00183

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 30-34
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1, 2 and 19
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 30-34

Claims 30-34 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/ Rule 39.1..(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Continuation of Box I.2

Claims Nos.: 1, 2 and 19

Claims 1, 2 and 19 do not meet the requirements of PCT Article 6. The application is directed to fusidic acid derivatives, and fusidic acid has a methyl group in position 8. The formulas 1 and 1a are not substituted in this position. In claim 19, which is dependent on claim 1, fusidic acid derivatives are claimed. The claims are therefore not clear and concise.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00183

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